

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problems Mailbox.**



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>A61K 31/165, 31/215, 31/33, 31/405, 31/415, 31/42, 31/425, 31/44, 31/47, 31/505, 31/53, 31/535, 31/54</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/17267</b>  <b>(43) International Publication Date:</b> 30 April 1998 (30.04.98)																																	
<b>(21) International Application Number:</b> PCT/US97/18864  <b>(22) International Filing Date:</b> 23 October 1997 (23.10.97)  <b>(30) Priority Data:</b> <table border="0"> <tr><td>08/736,318</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr> <tr><td>08/735,873</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr> <tr><td>08/735,881</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr> <tr><td>08/736,222</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr> <tr><td>08/736,221</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr> <tr><td>08/735,870</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr> <tr><td>08/735,876</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr> <tr><td>08/736,220</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr> <tr><td>08/736,319</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr> <tr><td>08/735,874</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr> <tr><td>08/736,228</td><td>23 October 1996 (23.10.96)</td><td>US</td></tr> </table> <b>(71) Applicants (for all designated States except US):</b> ZYMOGENETICS, INC. [US/US]; 1201 Eastlake Avenue East, Seattle, WA 98102 (US). OSTEOSCREEN, INC. [US/US]; Suite 201, 2040 Babcock Road, San Antonio, TX 78229 (US). UNIVERSITY OF TEXAS AUSTIN [US/US]; 201 W. 7th Street, Austin, TX 78701 (US).		08/736,318	23 October 1996 (23.10.96)	US	08/735,873	23 October 1996 (23.10.96)	US	08/735,881	23 October 1996 (23.10.96)	US	08/736,222	23 October 1996 (23.10.96)	US	08/736,221	23 October 1996 (23.10.96)	US	08/735,870	23 October 1996 (23.10.96)	US	08/735,876	23 October 1996 (23.10.96)	US	08/736,220	23 October 1996 (23.10.96)	US	08/736,319	23 October 1996 (23.10.96)	US	08/735,874	23 October 1996 (23.10.96)	US	08/736,228	23 October 1996 (23.10.96)	US	<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> ORME, Mark, W. [US/US]; 636 N.W. 98th Street, Seattle, WA 98117 (US). BAINBUR, Nand [IN/US]; 13919 57th Place West, Edmonds, WA 98026 (US). ROBBINS, Kirk, G. [US/US]; 1200 Grant Avenue South #Y-304, Renton, WA 98055 (US). HARRIS, Scott, M. [US/US]; 6825 31st Avenue N.E., Seattle, WA 98815 (US). KONTOTIANNI, Maria [GR/US]; 769 Hayes Street #504, Seattle, WA 98109 (US). HURLEY, Laurence, H. [US/US]; 5915 Northwest Place, Austin, TX 78731 (US). KERWIN, Sean, M. [US/US]; 703 Ivy Court, Round Rock, TX 78681 (US). MUNDY, Gregory, R. [US/US]; 3719 Morgan's Creek, San Antonio, TX 78230 (US). PETRIE, Charles [US/US]; 18459 N.E. 196th Place, Woodinville, WA 98072 (US).  <b>(74) Agents:</b> MURASHIGE, Kate, H. et al.; Morrison & Foerster LLP, 2000 Pennsylvania Avenue, N.W., Washington, DC 20006-1888 (US).  <b>(81) Designated States:</b> AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
08/736,318	23 October 1996 (23.10.96)	US																																	
08/735,873	23 October 1996 (23.10.96)	US																																	
08/735,881	23 October 1996 (23.10.96)	US																																	
08/736,222	23 October 1996 (23.10.96)	US																																	
08/736,221	23 October 1996 (23.10.96)	US																																	
08/735,870	23 October 1996 (23.10.96)	US																																	
08/735,876	23 October 1996 (23.10.96)	US																																	
08/736,220	23 October 1996 (23.10.96)	US																																	
08/736,319	23 October 1996 (23.10.96)	US																																	
08/735,874	23 October 1996 (23.10.96)	US																																	
08/736,228	23 October 1996 (23.10.96)	US																																	
<b>(54) Title:</b> COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS  <b>(57) Abstract</b>  <p>Compounds containing two aromatic systems covalently linked through a linker containing one or more atoms, or "linker" defined as including a covalent bond <i>per se</i> so as to space the aromatic systems at a distance 1.5-15Å, are effective in treating conditions associated with bone deficits. The compounds can be administered to vertebrate subjects alone or in combination with additional agents that promote bone growth or that inhibit bone resorption. They can be screened for activity prior to administration by assessing their ability to effect the transcription of a reporter gene coupled to a promoter associated with a bone morphogenetic protein and/or their ability to stimulate calvarial growth in model animal systems.</p>																																			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS

### Technical Field

5           The invention relates to compositions and methods for use in limiting undesired bone loss in a vertebrate at risk of such bone loss, in treating conditions that are characterized by undesired bone loss or by the need for bone growth, in treating fractures, and in treating cartilage disorders. More specifically, the invention concerns the use of specific classes of compounds identified or characterized by a high  
10           throughput screening assay.

### Background Art

          Bone is not a static tissue. It is subject to constant breakdown and resynthesis in a complex process mediated by osteoblasts, which produce new bone, and  
15           osteoclasts, which destroy bone. The activities of these cells are regulated by a large number of cytokines and growth factors, many of which have now been identified and cloned. Mundy has described the current knowledge related to these factors (Mundy, G.R. *Clin Orthop* 324:24-28, 1996; Mundy, G.R. *J Bone Miner Res* 8:S505-10, 1993).

20           Although there is a great deal of information available on the factors which influence the breakdown and resorption of bone, information on growth factors which stimulate the formation of new bone is more limited. Investigators have searched for sources of such activities, and have found that bone tissue itself is a storehouse for factors which have the capacity for stimulating bone cells. Thus, extracts of bovine  
25           bone tissue obtained from slaughterhouses contain not only structural proteins which are responsible for maintaining the structural integrity of bone, but also biologically active bone growth factors which can stimulate bone cells to proliferate. Among these latter factors are transforming growth factor  $\beta$ , the heparin-binding growth factors (acidic and basic fibroblast growth factor), the insulin-like growth factors (insulin-like  
30           growth factor I and insulin-like growth factor II), and a recently described family of

proteins called bone morphogenetic proteins (BMPs). All of these growth factors have effects on other types of cells, as well as on bone cells.

The BMPs are novel factors in the extended transforming growth factor  $\beta$  superfamily. They were first identified by Wozney J. *et al. Science* (1988) 242:1528-34, using gene cloning techniques, following earlier descriptions characterizing the biological activity in extracts of demineralized bone (Urist M. *Science* (1965) 150:893-99). Recombinant BMP2 and BMP4 can induce new bone formation when they are injected locally into the subcutaneous tissues of rats (Wozney J. *Molec Reprod Dev* (1992) 32:160-67). These factors are expressed by normal osteoblasts as they differentiate, and have been shown to stimulate osteoblast differentiation and bone nodule formation *in vitro* as well as bone formation *in vivo* (Harris S. *et al. J. Bone Miner Res* (1994) 9:855-63). This latter property suggests potential usefulness as therapeutic agents in diseases which result in bone loss.

The cells which are responsible for forming bone are osteoblasts. As osteoblasts differentiate from precursors to mature bone-forming cells, they express and secrete a number of enzymes and structural proteins of the bone matrix, including Type-1 collagen, osteocalcin, osteopontin and alkaline phosphatase (Stein G. *et al. Curr Opin Cell Biol* (1990) 2:1018-27; Harris S. *et al. (1994), supra*). They also synthesize a number of growth regulatory peptides which are stored in the bone matrix, and are presumably responsible for normal bone formation. These growth regulatory peptides include the BMPs (Harris S. *et al. (1994), supra*). In studies of primary cultures of fetal rat calvarial osteoblasts, BMPs 1, 2, 3, 4, and 6 are expressed by cultured cells prior to the formation of mineralized bone nodules (Harris S. *et al. (1994), supra*). Like alkaline phosphatase, osteocalcin and osteopontin, the BMPs are expressed by cultured osteoblasts as they proliferate and differentiate.

Although the BMPs are potent stimulators of bone formation *in vitro* and *in vivo*, there are disadvantages to their use as therapeutic agents to enhance bone healing. Receptors for the bone morphogenetic proteins have been identified in many tissues, and the BMPs themselves are expressed in a large variety of tissues in specific temporal and spatial patterns. This suggests that BMPs may have effects on many

tissues other than bone, potentially limiting their usefulness as therapeutic agents when administered systemically. Moreover, since they are peptides, they would have to be administered by injection. These disadvantages impose severe limitations to the development of BMPs as therapeutic agents.

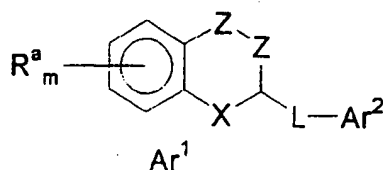
5           There is a plethora of conditions which are characterized by the need to enhance bone formation. Perhaps the most obvious is the case of bone fractures, where it would be desirable to stimulate bone growth and to hasten and complete bone repair. Agents that enhance bone formation would also be useful in facial reconstruction procedures. Other bone deficit conditions include bone segmental  
10 defects, periodontal disease, metastatic bone disease, osteolytic bone disease and conditions where connective tissue repair would be beneficial, such as healing or regeneration of cartilage defects or injury. Also of great significance is the chronic condition of osteoporosis, including age-related osteoporosis and osteoporosis associated with postmenopausal hormone status. Other conditions characterized by  
15 the need for bone growth include primary and secondary hyperparathyroidism, disuse osteoporosis, diabetes-related osteoporosis, and glucocorticoid-related osteoporosis. In addition, or alternatively, the compounds of the present invention may modulate metabolism, proliferation and/or differentiation of normal or aberrant cells or tissues.

          There are currently no satisfactory pharmaceutical approaches to managing any  
20 of these conditions. Bone fractures are still treated exclusively using casts, braces, anchoring devices and other strictly mechanical means. Further bone deterioration associated with postmenopausal osteoporosis has been decreased or prevented with estrogens or bisphosphonates.

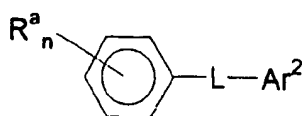
          US Patent 5, 280, 040 discloses a class of compounds which are 3, 4-diaryl  
25 chromans. These compounds can be considered derivatives of 2,3,4 triphenyl butanol, where the hydroxy at the 1-position forms an ether with the ortho position of the phenyl group substituted at the 4-position of the butanol. The parent 3,4-diaryl chromans do not contain nitrogen atoms in the aromatic moieties or their linkers. A preferred compound, centchroman, contains a nitrogen substituent only in one of the

substituents on a phenyl moiety. These compounds are disclosed in the '040 patent as useful in the treatment of osteoporosis.

In addition, the PCT application WO97/15308 published 1 May 1997 describes a number of classes of compounds that are active in the screening assay described  
 5 below and are useful in treating bone disorders. These compounds, generically, are of the formulae



- wherein  $R^a$  is a non-interfering substituent;  
 10  $m$  is an integer of 0-4;  
 each dotted line represents an optional  $\pi$ -bond;  
 each  $Z$  is independently N, NR, O, S, CR or  $CR_2$ , where each R is independently H or alkyl (1-6C);  
 X is O, S, SO or  $SO_2$ ;  
 15 L is a flexible linker; and  
 $Ar^2$  is a substituted or unsubstituted 6-membered aromatic ring; or:



- wherein  $R^a$  is a non-interfering substituent;  
 $n$  is an integer of 0 and 5;  
 20 L is a flexible linker which does not contain nitrogen or is a constrained linker;  
 and  
 $Ar^2$  is a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

There remains a need for additional compositions which can ameliorate the  
 25 effects of abnormalities in bone formation or resorption. The present invention

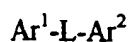
expands the repertoire of compounds useful for limiting or treating bone deficit conditions, and for other uses that should be apparent to those skilled in the art from the teachings herein.

5    Disclosure of the Invention

          The invention provides compounds that can be administered as ordinary pharmaceuticals and have the metabolic effect of enhancing bone growth or inhibiting resorption. The compounds of the invention can be identified using an assay for their ability to activate control elements associated with bone anabolic factors. Thus, the  
10   invention is directed to methods and compositions for treating bone disorders, which methods and compositions use, as active ingredients, compounds wherein two aromatic systems are coupled so as to be spaced apart from each other by about 1.5 to about 15 Angstroms. The thus-linked systems (including the linker coupling them) preferably include at least one nitrogen atom.

15       Therefore, the compounds useful in the invention can be described as having the formula  $\text{Ar}^1\text{-linker-Ar}^2$ , wherein each of  $\text{Ar}^1$  and  $\text{Ar}^2$  is independently an aromatic system and the linker portion of the formula spaces  $\text{Ar}^1$  and  $\text{Ar}^2$  apart by a distance of approximately 1.5-15 Angstroms.  $\text{Ar}^1$ ,  $\text{Ar}^2$  and the linker may optionally be substituted with non interfering substituents. In the useful compounds, there is  
20   preferably at least one nitrogen atom in either  $\text{Ar}^1$ ,  $\text{Ar}^2$  and/or the linker, independent of any substituents thereon. Preferably, the compounds of the invention contain at least one additional heteroatom selected from the group consisting of N, S and O, independent of any substituent.

          Thus, in one aspect, the invention is directed to a method to treat a condition in  
25   a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of certain compounds of the formula:





wherein each of Ar<sup>1</sup> and Ar<sup>2</sup> is independently substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, a substituted or unsubstituted aromatic system containing a 6-membered heterocycle, or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and

5 L is a linker that provides spacing of 1.5-15Å.

In other aspects, the invention relates to pharmaceutical compositions for use in the method, and to the compounds for use in preparing a medicament for use in the method.

#### 10 Brief Description of the Drawings

Figure 1 gives a schematic representation of the compounds used as active ingredients in the methods and compositions of the invention.

Figure 2 shows the dose response curve for a positive control compound, designated 59-0008.

15 Figures 3 and 4 show illustrative compounds of the invention and the results obtained with them in an *in vitro* test for stimulation of bone growth.

Figures 5A, 5B and 5C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0072.

20 Figures 6A, 6B and 6C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 50-0197.

Figure 7 shows structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0145.

Figures 8A, 8B and 8C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0045.

25 Figure 9 shows the results in an *ex vivo* calvarial assay for various compounds of the invention.

Figure 10 shows the increase in bone volume effected by subcutaneous administration of compound 59-0145 in the OVX *in vivo* assay.

30 Figure 11 is a graphical representation of percent increase in trabecular bone in ovariectomized rats treated with compound 59-0145.

Figure 12 presents graphs showing results of qCT and bone histomorphometri and serum osteocalcin levels in rats treated with compound 59-0145.

Figure 13 (41 pages) is a list of compounds used in screening for bone morphogenic activity according to the screening assay set forth herein.

5

#### Modes of Carrying Out the Invention

A rapid throughput screening test for compounds capable of stimulating expression of a reporter gene linked to a BMP promoter (a surrogate for the production of bone morphogenetic factors that are endogenously produced) is described in WO96/38590 published 5 December 1996, the contents of which are incorporated herein by reference. This assay is also described as a portion of a study of immortalized murine osteoblasts (derived from a mouse expressing a transgene composed of a BMP2 promoter driving expression of T-antigen) in Ghosh-Choudhery, N. *et al. Endocrinology* (1996) 137:331-39. In this study, the immortalized cells were stably transfected with a plasmid containing a luciferase reporter gene driven by a mouse BMP2 promoter (-2736/114 bp), and responded in a dose-dependent manner to recombinant human BMP2.

Briefly, the assay utilizes cells transformed permanently or transiently with constructs in which the promoter of a bone morphogenetic protein, specifically BMP2 or BMP4, is coupled to a reporter gene, typically luciferase. These transformed cells are then evaluated for the production of the reporter gene product; compounds that activate the BMP promoter will drive production of the reporter protein, which can be readily assayed. Over 40,000 compounds have been subjected to this rapid screening technique, and only a very small percentage are able to elicit a level of production of luciferase 5-fold greater than that produced by vehicle. Compounds that activate the BMP promoter share certain structural characteristics not present in inactive compounds. The active compounds ("BMP promoter-active compounds" or "active compounds") are useful in promoting bone or cartilage growth, and thus in the treatment of vertebrates in need of bone or cartilage growth.

BMP promoter-active compounds can be examined in a variety of other assays that test specificity and toxicity. For instance, nonBMP promoters or response elements can be linked to a reporter gene and inserted into an appropriate host cell. Cytotoxicity can be determined by visual or microscopic examination of BMP  
5 promoter- and/or nonBMP promoter-reporter gene-containing cells, for instance. Alternatively, nucleic acid and/or protein synthesis by the cells can be monitored. For *in vivo* assays, tissues may be removed and examined visually or microscopically, and optionally examined in conjunction with dyes or stains that facilitate histologic examination. In assessing *in vivo* assay results, it may also be useful to examine  
10 biodistribution of the test compound, using conventional medicinal chemistry/animal model techniques.

As used herein, "limit" or "limiting" and "treat" or "treatment" are interchangeable terms. The terms include a postponement of development of bone deficit symptoms and/or a reduction in the severity of such symptoms that will or are  
15 expected to develop. The terms further include ameliorating existing bone or cartilage deficit symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, preventing or reversing bone resorption and/or encouraging bone growth. Thus, the terms denote that a beneficial result has been conferred on a vertebrate subject with a cartilage, bone or skeletal deficit, or with  
20 the potential to develop such deficit.

By "bone deficit" is meant an imbalance in the ratio of bone formation to bone resorption, such that, if unmodified, the subject will exhibit less bone than desirable, or the subject's bones will be less intact and coherent than desired. Bone deficit may also result from fracture, from surgical intervention or from dental or periodontal disease.  
25 By "cartilage defect" is meant damaged cartilage, less cartilage than desired, or cartilage that is less intact and coherent than desired.

Representative uses of the compounds of the present invention include: repair of bone defects and deficiencies, such as those occurring in closed, open and nonunion fractures; prophylactic use in closed and open fracture reduction; promotion of bone  
30 healing in plastic surgery; stimulation of bone ingrowth into noncemented prosthetic

joints and dental implants; elevation of peak bone mass in premenopausal women; treatment of growth deficiencies; treatment of periodontal disease and defects, and other tooth repair processes; increase in bone formation during distraction osteogenesis; and treatment of other skeletal disorders, such as age-related osteoporosis, postmenopausal  
5 osteoporosis, glucocorticoid-induced osteoporosis or disuse osteoporosis and arthritis. The compounds of the present invention can also be useful in repair of congenital, trauma-induced or surgical resection of bone (for instance, for cancer treatment), and in cosmetic surgery. Further, the compounds of the present invention can be used for limiting or treating cartilage defects or disorders, and may be useful in wound healing  
10 or tissue repair.

Bone or cartilage deficit or defect can be treated in vertebrate subjects by administering compounds of the invention which have been identified through suitable screening assays and which exhibit certain structural characteristics. The compositions of the invention may be administered systemically or locally. For systemic use, the  
15 compounds herein are formulated for parenteral (e.g., intravenous, subcutaneous, intramuscular, intraperitoneal, intranasal or transdermal) or enteral (e.g., oral or rectal) delivery according to conventional methods. Intravenous administration will be by a series of injections or by continuous infusion over an extended period. Administration by injection or other routes of discretely spaced administration will generally be  
20 performed at intervals ranging from weekly to once to three times daily. Alternatively, the compounds disclosed herein may be administered in a cyclical manner (administration of disclosed compound; followed by no administration; followed by administration of disclosed compound, and the like). Treatment will continue until the desired outcome is achieved. In general, pharmaceutical formulations will include a  
25 compound of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water, borate-buffered saline containing trace metals or the like. Formulations may further include one or more excipients, preservatives, solubilizers, buffering agents, albumin to prevent protein loss on vial surfaces, lubricants, fillers, stabilizers, etc. Methods of formulation are well  
30 known in the art and are disclosed, for example, in Remington's Pharmaceutical

Sciences, Gennaro, ed., Mack Publishing Co., Easton PA, 1990, which is incorporated herein by reference. Pharmaceutical compositions for use within the present invention can be in the form of sterile, nonpyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art. Local administration may be by injection at the site of injury or defect, or by insertion or attachment of a solid carrier at the site, or by direct, topical application of a viscous liquid. For local administration, the delivery vehicle preferably provides a matrix for the growing bone or cartilage, and more preferably is a vehicle that can be absorbed by the subject without adverse effects.

Delivery of compounds herein to wound sites may be enhanced by the use of controlled-release compositions, such as those described in WIPO publication WO 93/20859, which is incorporated herein by reference in its entirety. Films of this type are particularly useful as coatings for prosthetic devices and surgical implants. The films may, for example, be wrapped around the outer surfaces of surgical screws, rods, pins, plates and the like. Implantable devices of this type are routinely used in orthopedic surgery. The films can also be used to coat bone filling materials, such as hydroxyapatite blocks, demineralized bone matrix plugs, collagen matrices and the like. In general, a film or device as described herein is applied to the bone at the fracture site. Application is generally by implantation into the bone or attachment to the surface using standard surgical procedures.

In addition to the copolymers and carriers noted above, the biodegradable films and matrices may include other active or inert components. Of particular interest are those agents that promote tissue growth or infiltration, such as growth factors. Exemplary growth factors for this purpose include epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factors (TGFs), parathyroid hormone (PTH), leukemia inhibitory factor (LIF), and insulin-like growth factors (IGFs). Agents that promote bone growth, such as bone morphogenetic proteins (U.S. Patent No. 4,761,471; PCT Publication WO 90/11366), osteogenin (Sampath *et al. Proc. Natl. Acad. Sci. USA* (1987) 84:7109-13) and NaF (Tencer *et al. J. Biomed. Mat. Res.* (1989) 23: 571-89) are also preferred.

Biodegradable films or matrices include calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyanhydrides, bone or dermal collagen, pure proteins, extracellular matrix components and combinations thereof. Such biodegradable materials may be used in combination with nonbiodegradable materials, to provide desired mechanical, cosmetic or tissue or matrix interface properties.

Alternative methods for delivery of compounds of the present invention include use of ALZET osmotic minipumps (Alza Corp., Palo Alto, CA); sustained release matrix materials such as those disclosed in Wang *et al.* (PCT Publication WO 90/11366); electrically charged dextran beads, as disclosed in Bao *et al.* (PCT Publication WO 92/03125); collagen-based delivery systems, for example, as disclosed in Ksander *et al. Ann. Surg.* (1990) 211(3):288-94; methylcellulose gel systems, as disclosed in Beck *et al. J. Bone Min. Res.* (1991) 6(11):1257-65; and alginate-based systems, as disclosed in Edelman *et al. Biomaterials* (1991) 12:619-26. Other methods well known in the art for sustained local delivery in bone include porous coated metal prostheses that can be impregnated and solid plastic rods with therapeutic compositions incorporated within them.

The compounds of the present invention may also be used in conjunction with agents that inhibit bone resorption. Antiresorptive agents, such as estrogen, bisphosphonates and calcitonin, are preferred for this purpose. More specifically, the compounds disclosed herein may be administered for a period of time (for instance, months to years) sufficient to obtain correction of a bone deficit condition. Once the bone deficit condition has been corrected, the vertebrate can be administered an anti-resorptive compound to maintain the corrected bone condition. Alternatively, the compounds disclosed herein may be administered with an anti-resorptive compound in a cyclical manner (administration of disclosed compound, followed by anti-resorptive, followed by disclosed compound, and the like).

In additional formulations, conventional preparations such as those described below may be used.

Aqueous suspensions may contain the active ingredient in admixture with pharmacologically acceptable excipients, comprising suspending agents, such as methyl

cellulose; and wetting agents, such as lecithin, lysolethicin or long-chain fatty alcohols. The said aqueous suspensions may also contain preservatives, coloring agents, flavoring agents and sweetening agents in accordance with industry standards.

Preparations for topical and local application comprise aerosol sprays, lotions,  
5 gels and ointments in pharmaceutically appropriate vehicles which may comprise lower aliphatic alcohols, polyglycols such as glycerol, polyethylene glycol, esters of fatty acids, oils and fats, and silicones. The preparations may further comprise antioxidants, such as ascorbic acid or tocopherol, and preservatives, such as p-hydroxybenzoic acid esters.

10 Parenteral preparations comprise particularly sterile or sterilized products. Injectable compositions may be provided containing the active compound and any of the well known injectable carriers. These may contain salts for regulating the osmotic pressure.

If desired, the osteogenic agents can be incorporated into liposomes by any of  
15 the reported methods of preparing liposomes for use in treating various pathogenic conditions. The present compositions may utilize the compounds noted above incorporated in liposomes in order to direct these compounds to macrophages, monocytes, other cells and tissues and organs which take up the liposomal composition. The liposome-incorporated compounds of the invention can be utilized  
20 by parenteral administration, to allow for the efficacious use of lower doses of the compounds. Ligands may also be incorporated to further focus the specificity of the liposomes.

Suitable conventional methods of liposome preparation include, but are not limited to, those disclosed by Bangham, A.D. *et al. J Mol Biol* (1965) 23:238-252,  
25 Olson, F. *et al. Biochim Biophys Acta* (1979) 557:9-23, Szoka, F. *et al. Proc Natl Acad Sci USA* (1978) 75:4194-4198, Mayhew, E. *et al. \_\_\_\_\_* (1984) 775:169-175, Kim, S. *et al. Biochim Biophys Acta* (1983) 728:339:348, and Mayer, *et al. Biochim Biophys Acta* (1986) 858:161-168.

The liposomes may be made from the present compounds in combination with  
30 any of the conventional synthetic or natural phospholipid liposome materials including

phospholipids from natural sources such as egg, plant or animal sources such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, sphingomyelin, phosphatidylserine, or phosphatidylinositol. Synthetic phospholipids that may also be used, include, but are not limited to: dimyristoylphosphatidylcholine, 5 dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine, and the corresponding synthetic phosphatidylethanolamines and phosphatidylglycerols. Cholesterol or other sterols, cholesterol hemisuccinate, glycolipids, cerebroside, fatty acids, gangliosides, sphingolipids, 1,2-bis(oleoyloxy)-3-(trimethyl ammonio) propane (DOTAP), N-[1-(2,3-dioleoyl) propyl-N,N,N-trimethylammonium chloride (DOTMA), and other 10 cationic lipids may be incorporated into the liposomes, as is known to those skilled in the art. The relative amounts of phospholipid and additives used in the liposomes may be varied if desired. The preferred ranges are from about 60 to 90 mole percent of the phospholipid; cholesterol, cholesterol hemisuccinate, fatty acids or cationic lipids may 15 be used in amounts ranging from 0 to 50 mole percent. The amounts of the present compounds incorporated into the lipid layer of liposomes can be varied with the concentration of their lipids ranging from about 0.01 to about 50 mole percent.

Using conventional methods, approximately 20 to 30% of the compound present in solution can be entrapped in liposomes; thus, approximately 70 to 80% of 20 the active compound is wasted. In contrast, where the compound is incorporated into liposomes, virtually all of the compound is incorporated into the liposome, and essentially none of the active compound is wasted.

The liposomes with the above formulations may be made still more specific for their intended targets with the incorporation of monoclonal antibodies or other ligands 25 specific for a target. For example, monoclonal antibodies to the BMP receptor may be incorporated into the liposome by linkage to phosphatidylethanolamine (PE) incorporated into the liposome by the method of Leserman, L. *et al. Nature* (1980) 288:602-604.

Veterinary uses of the disclosed compounds are also contemplated. Such uses 30 would include limitation or treatment of bone or cartilage deficits or defects in



domestic animals, livestock and thoroughbred horses. The compounds described herein can also modify a target tissue or organ environment, so as to attract bone-forming cells to an environment in need of such cells.

The compounds of the present invention may also be used to stimulate growth  
5 of bone-forming cells or their precursors, or to induce differentiation of bone-forming cell precursors, either *in vitro* or *ex vivo*. As used herein, the term "precursor cell" refers to a cell that is committed to a differentiation pathway, but that generally does not express markers or function as a mature, fully differentiated cell. As used herein, the term "mesenchymal cells" or "mesenchymal stem cells" refers to pluripotent  
10 progenitor cells that are capable of dividing many times, and whose progeny will give rise to skeletal tissues, including cartilage, bone, tendon, ligament, marrow stroma and connective tissue (see A. Caplan *J. Orthop. Res.* (1991) 9:641-50). As used herein, the term "osteogenic cells" includes osteoblasts and osteoblast precursor cells. More particularly, the disclosed compounds are useful for stimulating a cell population  
15 containing marrow mesenchymal cells, thereby increasing the number of osteogenic cells in that cell population. In a preferred method, hematopoietic cells are removed from the cell population, either before or after stimulation with the disclosed compounds. Through practice of such methods, osteogenic cells may be expanded. The expanded osteogenic cells can be infused (or reinfused) into a vertebrate subject in  
20 need thereof. For instance, a subject's own mesenchymal stem cells can be exposed to compounds of the present invention *ex vivo*, and the resultant osteogenic cells could be infused or directed to a desired site within the subject, where further proliferation and/or differentiation of the osteogenic cells can occur without immunorejection. Alternatively, the cell population exposed to the disclosed compounds may be  
25 immortalized human fetal osteoblastic or osteogenic cells. If such cells are infused or implanted in a vertebrate subject, it may be advantageous to "immunoprotect" these nonself cells, or to immunosuppress (preferably locally) the recipient to enhance transplantation and bone or cartilage repair.

Within the present invention, an "effective amount" of a composition is that  
30 amount which produces a statistically significant effect. For example, an "effective

- amount" for therapeutic uses is the amount of the composition comprising an active compound herein required to provide a clinically significant increase in healing rates in fracture repair; reversal of bone loss in osteoporosis; reversal of cartilage defects or disorders; prevention or delay of onset of osteoporosis; stimulation and/or
- 5 augmentation of bone formation in fracture nonunions and distraction osteogenesis; increase and/or acceleration of bone growth into prosthetic devices; and repair of dental defects. Such effective amounts will be determined using routine optimization techniques and are dependent on the particular condition to be treated, the condition of the patient, the route of administration, the formulation, and the judgment of the
- 10 practitioner and other factors evident to those skilled in the art. The dosage required for the compounds of the invention (for example, in osteoporosis where an increase in bone formation is desired) is manifested as a statistically significant difference in bone mass between treatment and control groups. This difference in bone mass may be seen, for example, as a 5-20% or more increase in bone mass in the treatment group.
- 15 Other measurements of clinically significant increases in healing may include, for example, tests for breaking strength and tension, breaking strength and torsion, 4-point bending, increased connectivity in bone biopsies and other biomechanical tests well known to those skilled in the art. General guidance for treatment regimens is obtained from experiments carried out in animal models of the disease of interest.
- 20 The dosage of the compounds of the invention will vary according to the extent and severity of the need for treatment, the activity of the administered compound, the general health of the subject, and other considerations well known to the skilled artisan. Generally, they can be administered to a typical human on a daily basis on an oral dose of about 0.1 mg/kg-1000 mg/kg, and more preferably from about 1 mg/kg to
- 25 about 200 mg/kg. The parenteral dose will appropriately be 20-100% of the oral dose.

#### Screening Assays

The osteogenic activity of the compounds used in the methods of the invention can be verified using *in vitro* screening techniques, such as the assessment of

transcription of a reporter gene coupled to a bone morphogenetic protein-associated promoter, as described above, or in alternative assays such as the following:

Technique for Neonatal Mouse Calvarial Assay (*In vitro*)

5        This assay is similar to that described by Gowen M. & Mundy G. *J Immunol* (1986) 136:2478-82. Briefly, four days after birth, the front and parietal bones of ICR Swiss white mouse pups are removed by microdissection and split along the sagittal suture. The bones are incubated in BGJb medium (Irvine Scientific, Santa Ana, CA) plus 0.02% (or lower concentration)  $\beta$ -methylcyclodextrin, wherein the medium also  
10       contains test or control substances, at 37°C in a humidified atmosphere of 5% CO<sub>2</sub> and 95% air for 96 hours.

         Following this, the bones are removed from the incubation media and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1 week, processed through graded alcohols; and embedded in paraffin wax. Three  $\mu$ m sections  
15       of the calvaria are prepared. Representative sections are selected for histomorphometric assessment of bone formation and bone resorption. Bone changes are measured on sections cut 200  $\mu$ m apart. Osteoblasts and osteoclasts are identified by their distinctive morphology.

         Other auxillary assays can be used as controls to determine nonBMP promoter-mediated effects of test compounds. For example, mitogenic activity can be measured  
20       using screening assays featuring a serum-response element (SRE) as a promoter and a luciferase reporter gene. More specifically, these screening assays can detect signalling through SRE-mediated pathways, such as the protein kinase C pathway. For instance, an osteoblast activator SRE-luciferase screen and an insulin mimetic SRE-luciferase  
25       screen are useful for this purpose. Similarly, test compound stimulation of cAMP response element (CRE)-mediated pathways can also be assayed. For instance, cells transfected with receptors for PTH and calcitonin (two bone-active agents) can be used in CRE-luciferase screens to detect elevated cAMP levels. Thus, the BMP promoter specificity of a test compound can be examined through use of these types of  
30       auxillary assays.

### In vivo Assay of Effects of Compounds on Murine Calvarial Bone Growth

Male ICR Swiss white mice, aged 4-6 weeks and weighing 13-26 gm, are employed, using 4-5 mice per group. The calvarial bone growth assay is performed as described in PCT application WO 95/24211. Briefly, the test compound or appropriate control vehicle is injected into the subcutaneous tissue over the right calvaria of normal mice. Typically, the control vehicle is the vehicle in which the compound was solubilized, and is PBS containing 5% DMSO or is PBS containing Tween (2  $\mu$ l/10 ml). The animals are sacrificed on day 14 and bone growth measured by histomorphometry. Bone samples for quantitation are cleaned from adjacent tissues and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1-3 weeks, processed through graded alcohols; and embedded in paraffin wax. Three to five  $\mu$ m sections of the calvaria are prepared, and representative sections are selected for histomorphometric assessment of the effects on bone formation and bone resorption. Sections are measured by using a camera lucida attachment to trace directly the microscopic image onto a digitizing plate. Bone changes are measured on sections cut 200  $\mu$ m apart, over 4 adjacent 1x1 mm fields on both the injected and noninjected sides of the calvaria. New bone is identified by its characteristic woven structure, and osteoclasts and osteoblasts are identified by their distinctive morphology. Histomorphometry software (OsteoMeasure, Osteometrix, Inc., Atlanta) is used to process digitizer input to determine cell counts and measure areas or perimeters.

### Additional In Vivo Assays

Lead compounds can be further tested in intact animals using an *in vivo*, dosing assay. Prototypical dosing may be accomplished by subcutaneous, intraperitoneal or oral administration, and may be performed by injection, sustained release or other delivery techniques. The time period for administration of test compound may vary (for instance, 28 days as well as 35 days may be appropriate). An exemplary, *in vivo* subcutaneous dosing assay may be conducted as follows:

In a typical study, 70 three-month-old female Sprague-Dawley rats are weight-matched and divided into seven groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; a control group administered vehicle only; a PBS-treated control group; and a positive control group administered a compound (nonprotein or protein) known to promote bone growth. Three dosage levels of the compound to be tested are administered to the remaining three groups.

Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. All animals are injected with calcein nine days and two days before sacrifice (two injections of calcein administered each designated day). Weekly body weights are determined. At the end of the 35-day cycle, the animals are weighed and bled by orbital or cardiac puncture. Serum calcium, phosphate, osteocalcin, and CBCs are determined. Both leg bones (femur and tibia) and lumbar vertebrae are removed, cleaned of adhering soft tissue, and stored in 70% ethanol for evaluation, as performed by peripheral quantitative computed tomography (pqCT; Ferretti, J. *Bone* (1995) 17:353S-64S), dual energy X-ray absorptiometry (DEXA; Laval-Jeantet A. *et al. Calcif Tissue Intl* (1995) 56:14-18; J. Casez *et al. Bone and Mineral* (1994) 26:61-68) and/or histomorphometry. The effect of test compounds on bone remodeling can thus be evaluated.

Lead compounds also be tested in acute ovariectomized animals (prevention model) using an *in vivo* dosing assay. Such assays may also include an estrogen-treated group as a control. An exemplary subcutaneous dosing assay is performed as follows:

In a typical study, 80 three-month-old female Sprague-Dawley rats are weight-matched and divided into eight groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; three control groups (sham ovariectomized (sham OVX) + vehicle only; ovariectomized (OVX) + vehicle only; PBS-treated OVX); and a control OVX group that is administered a compound known to promote bone growth. Three dosage levels of the compound to be tested are administered to the remaining three groups of OVX animals.

Since ovariectomy (OVX) induces hyperphagia, all OVX animals are pair-fed with sham OVX animals throughout the 35 day study. Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. Alternatively, test compound can be formulated in implantable pellets that are implanted for 35 days, or may be administered orally, such as by gastric gavage. All animals, including sham OVX/vehicle and OVX/vehicle groups, are injected intraperitoneally with calcein nine days and two days before sacrifice (two injections of calcein administered each designated day, to ensure proper labeling of newly formed bone). Weekly body weights are determined. At the end of the 35-day cycle, the animals' blood and tissues are processed as described above.

Lead compounds may also be tested in chronic OVX animals (treatment model). An exemplary protocol for treatment of established bone loss in ovariectomized animals that can be used to assess efficacy of anabolic agents may be performed as follows. Briefly, 80 to 100 six month old female, Sprague-Dawley rats are subjected to sham surgery (sham OVX) or ovariectomy (OVX) at time 0, and 10 rats are sacrificed to serve as baseline controls. Body weights are recorded weekly during the experiment. After approximately 6 weeks of bone depletion (42 days), 10 sham OVX and 10 OVX rats are randomly selected for sacrifice as depletion period controls. Of the remaining animals, 10 sham OVX and 10 OVX rats are used as placebo-treated controls. The remaining OVX animals are treated with 3 to 5 doses of test drug for a period of 5 weeks (35 days). As a positive control, a group of OVX rats can be treated with an agent such as PTH, a known anabolic agent in this model (Kimmel *et al. Endocrinology* (1993) 132:1577-84). To determine effects on bone formation, the following procedure can be followed. The femurs, tibiae and lumbar vertebrae 1 to 4 are excised and collected. The proximal left and right tibiae are used for pqCT measurements, cancellous bone mineral density (BMD) (gravimetric determination), and histology, while the midshaft of each tibiae is subjected to cortical BMD or histology. The femurs are prepared for pqCT scanning of the midshaft prior to biomechanical testing. With respect to lumbar vertebrae (LV), LV2 are processed

for BMD (pqCT may also be performed); LV3 are prepared for undecalcified bone histology; and LV4 are processed for mechanical testing.

#### Nature of the Compounds Useful in the Invention

5 All of the compounds of the invention contain two aromatic systems,  $\text{Ar}^1$  and  $\text{Ar}^2$ , spaced apart by a linker at a distance of 1.5-15 Å, and may preferably contain at least one nitrogen atom. A summary of the structural features of the compounds included within the invention is shown in Figure 1.

As shown,  $\text{Ar}^1$  and  $\text{Ar}^2$  may include various preferred embodiments. These are  
10 selected from the group consisting of a substituted or unsubstituted aromatic ring system containing a 5-membered heterocycle; a substituted or unsubstituted aromatic ring system containing a six-membered heterocycle; a substituted or unsubstituted naphthalene moiety; and a substituted or unsubstituted benzene moiety. There are 16 possible combinations of these embodiments, if  $\text{Ar}^1$  and  $\text{Ar}^2$  are considered  
15 distinguishable. As will be clear, however, the designation of one aromatic system as  $\text{Ar}^1$  and the other as  $\text{Ar}^2$  is arbitrary; thus there are only ten possible combinations. However, for simplicity,  $\text{Ar}^1$  and  $\text{Ar}^2$  are designated separately with the realization that the choice is arbitrarily made. All linkers described herein if not palindromic, are considered to link  $\text{Ar}^1$  to  $\text{Ar}^2$  or *vice-versa* whether or not the complementary  
20 orientation is explicitly shown (as it is in some cases). Thus, if  $\text{Ar}^1$  and  $\text{Ar}^2$  are different and a linker is specified as -CONR-, it is understood that also included is the linker -NRCO- when the designations  $\text{Ar}^1$  and  $\text{Ar}^2$  are retained.

The noninterfering substituents on the aromatic system represented by  $\text{Ar}^1$  and the noninterfering substituents on the aromatic system represented by  $\text{Ar}^2$  are  
25 represented in the formulas herein by  $\text{R}^a$  and  $\text{R}^b$ , respectively. Generally, these substituents can be of wide variety. Among substituents that do not interfere with (and in some instances may be desirable for) the beneficial effect of the compounds of the invention on bone in treated subjects are included alkyl (1-6C, preferably lower alkyl 1-4C), including straight or branched-chain forms thereof, alkenyl (1-6C, preferably  
30 1-4C), alkynyl (1-6C, preferably 1-4C), all of which can be straight or branched chains

or are aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C) and may contain further substituents.  $R^a$  and  $R^b$  may also include halogens, (e.g. F, Cl, Br and I); siloxy, OR, SR,  $NR_2$ , OOCR, COOR, NCOR, NCOOR, and benzoyl,  $CF_3$ ,  $OCF_3$ ,  $SCF_3$ ,  $N(CF_3)_2$ , NO,  $NO_2$ , CN, SO,  $SO_2R$ ,  $SO_3R$  and the like, wherein R is alkyl (1-6C) or is H.

5 Similarly, these substituents may contain  $R'$  as a substitute for R wherein  $R'$  is aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C). Where  $R^a$  or  $R^b$  substituents are in adjacent positions in the aromatic system, they may combine to form a ring. Further, rings may be included in substituents which contain sufficient carbon and heteroatoms to provide this possibility.

10 The choice of noninterfering substituents depends on the overall nature of the system. For example, in compounds of the invention wherein two pyridine rings are linked through a saturated flexible linker, a  $CF_3$  substituent para to the linker in each of the pyridine rings is particularly preferred. In those systems wherein a quinoline is coupled through a flexible conjugated or nonconjugated linker to a phenyl substituent  
15 or to a naphthyl substituent, an amino group para to the linker in the phenyl or naphthyl moiety is preferred. Particularly preferred amino groups are dimethylamino and diethylamino. In systems wherein a benzothiazole is coupled to phenyl through a flexible linker, preferred substituents on the phenyl moiety include alkoxy or alkylthio in combination with halo, in particular, chloro. Also preferred is the presence of a  
20 diethylamino group in the phenyl moiety para to the position that is coupled to the linker. In general, the presence of a substituent in the phenyl moiety para to the position of joinder to the linker is preferred.

Generally, preferred noninterfering substituents include hydrocarbyl groups of 1-6C, including saturated and unsaturated, linear or branched hydrocarbyl as well as  
25 hydrocarbyl groups containing ring systems; halo groups, alkoxy, hydroxy, amino, monoalkyl- and dialkylamino where the alkyl groups are 1-6C, CN,  $CF_3$ ,  $OCF_3$  and COOR, and the like.

Although the number of  $R^a$  and  $R^b$  may typically be 0-4 (m) or 0-5 (n) depending on the available positions in the aromatic system, preferred embodiments



include those wherein the number of  $R^a$  is 0, 1 or 2 and of  $R^b$  is 0, 1, 2 or 3, particularly 1 or 2.

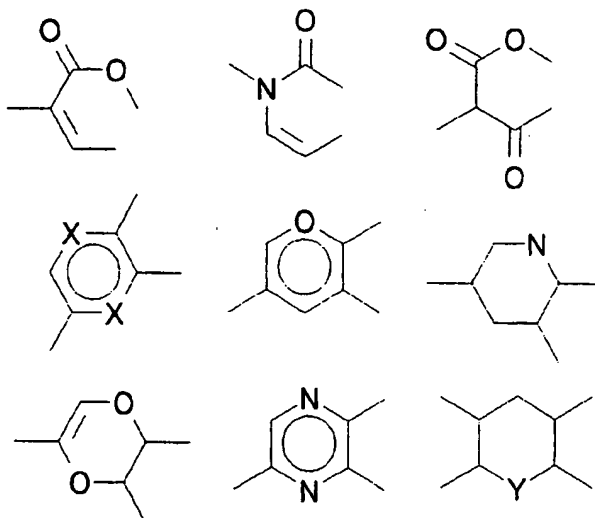
The linker group, L, may be a covalent bond or any group having a valence of at least two and covering a linear distance of from about 1.5 to about 15 Angstroms, including those that contain cyclic moieties, that meet this spatial requirement. Useful  
 5 linkers are divided, by definition herein, into three general categories: (1) flexible nonconjugating linkers, (2) flexible conjugating linkers, and (3) constrained linkers. The preferred choice of linker will depend on the choices for  $Ar^1$  and  $Ar^2$ .

As defined herein, *flexible nonconjugating* linkers are those that link only one  
 10 position of  $Ar^1$  to one position of  $Ar^2$ , and provide only a single covalent bond or a single chain between  $Ar^1$  and  $Ar^2$ . The chain may contain branches, but may not contain  $\pi$ -bonds (except in the branches) or cyclic portions in the chain. The linker atoms in the chain itself rotate freely around single covalent bonds, and thus the linker has more than two degrees of freedom. Particularly useful flexible nonconjugating  
 15 linkers, besides a covalent bond, are those of the formulas:  $-NR-$ ,  $-CR_2-$ ,  $-S-$ , or  $-O-$ , wherein R is H or alkyl (1-6C), more preferably H or lower alkyl (1-4C) and more preferably H. Also contemplated are those of the formulas:  $-NRCO-$ ,  $-CONR-$ ,  $-CR_2S-$ ,  $-SCR_2-$ ,  $-OCR_2-$ ,  $-CR_2O-$ ,  $-NRNR-$ ,  $-CR_2CR_2-$ ,  $-NRSO_2-$ ,  $-SO_2NR-$ ,  $-CR_2CO-$ ,  $-COCR_2-$ , and  $-NR-NR-CO-CR_2-$  and its complement  $-CR_2-CO-NR-NR-$ ,  
 20 or  $-NRCR_2CR_2NR-$  or the thiolated counterparts, and particularly  $-NHCR_2CR_2NH-$ , including the isosteres thereof, such as  $-NRNRCSNR-$  and  $-NRNRCONR-$ . Also contemplated are those of the formulas:  $-NH(CH_2)_2NH-$ ,  $-O(CR_2)_2O-$ , and  $-S(CR_2)_2S-$ , including the isosteres thereof. The optimum choice among flexible nonconjugating linkers is dependent on the nature of  $Ar^1$  and  $Ar^2$ .

25 *Flexible conjugating* linkers are those that link only one position of  $Ar^1$  to one position of  $Ar^2$ , but incorporate at least one double or triple bond or one or more cyclic systems in the chain itself and thus have only two degrees of freedom. A flexible conjugating linker may form a completely conjugated  $\pi$ -bond linking system between  $Ar^1$  and  $Ar^2$ , thus providing for co-planarity of  $Ar^1$  and  $Ar^2$ . Examples of useful  
 30 flexible conjugating linkers include:  $-RC=CR-$ ;  $-N=N-$ ;  $-C\equiv C-$ ;  $-RC=N-$ ;  $-N=CR-$ ;

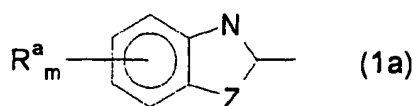
-NR-N=CR-, -NR-NR-CO-CR=CR-, -N=NCOCR<sub>2</sub>-, -N=NCSCR<sub>2</sub>-, -N=NCOCR<sub>2</sub>CR<sub>2</sub>-,  
 -N=NCONR-, -N=NCSNR-, and the like, where R is H or alkyl (1-6C); preferably H  
 or lower alkyl (1-4C); and more preferably H.

*Constrained* linkers are those that have more than one point of attachment to  
 5 either or both Ar<sup>1</sup> and Ar<sup>2</sup> and, thus, generally allow for only one degree of freedom.  
 Constrained linkers most frequently form fused 5- or 6-membered cyclic moieties with  
 Ar<sup>1</sup> and/or Ar<sup>2</sup> where either Ar<sup>1</sup> or Ar<sup>2</sup> has at least one substituent appropriately  
 positioned to form a second covalent bond with the linker, e.g., where Ar<sup>2</sup> is a phenyl  
 group with a reactive, ortho-positioned substituent, or is derivatized to the linker  
 10 directly at the ortho position. (Although the aromatic moieties should properly be  
 referred to as phenylene or naphthylene in such cases, generally the term "phenyl" or  
 "naphthyl" is used herein to include both monovalent and bivalent forms of these  
 moieties.) Examples of particularly useful constrained linkers include

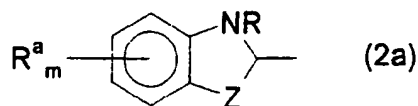


15 and the like, where X is O, N, S or CR, and Y is CR<sub>2</sub> or C=O.

In one class of preferred embodiments, Ar<sup>1</sup> is an aromatic system containing a  
 5-membered heterocycle, of the formula:



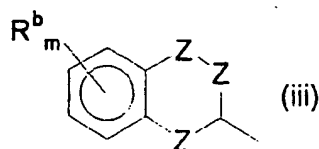
or



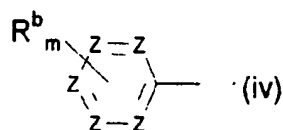
wherein Z is S, O, NR or -CR<sub>2</sub> in formula (1a) or CR in formula (2a), where each R is independently H or alkyl (1-6C), the dotted line represents an optional  $\pi$ -bond, each R<sup>a</sup> is independently a noninterfering substituent as defined above, and m is an integer of 0-4.

In general, Ar<sup>2</sup> is phenyl, naphthyl, or an aromatic system containing a 5- or 6-membered heterocyclic ring. All may be unsubstituted or substituted with noninterfering substituents, R<sup>b</sup>.

When Ar<sup>2</sup> is an aromatic system containing a six-membered heterocycle, the formula of said system is preferably:

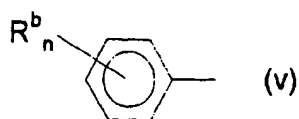


or



wherein each Z is independently a heteroatom selected from the group consisting of S, O and N; or is CR or CR<sub>2</sub>, the dotted lines represent optional  $\pi$ -bonds, each R<sup>b</sup> is independently a noninterfering substituent, and m is an integer of 0-4, with the proviso that at least one Z must be a heteroatom.

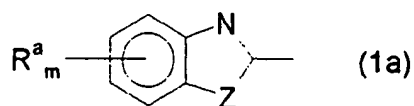
Ar<sup>2</sup> in these compounds may also have the formula



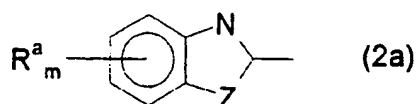
where  $R^b$  is a noninterfering substituent as defined above and  $n$  is an integer from 0 to 5.

Similarly, when  $Ar^2$  is naphthyl, it may contain 0-5  $R^b$  substitutions. When  $Ar^2$  is an aromatic system containing a 5-membered heterocycle, preferred forms are those as described for  $Ar^1$ .

Thus, in one set of preferred compounds,  $Ar^1$  is

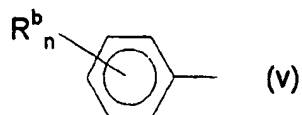


or



wherein each  $R^a$  is a noninterfering substituent,  $m$  is an integer of 0-4, the dotted line represents an optional  $\pi$  bond, and  $Z$  is O, S, NR or  $CR_2$  in formula (1) or is CR in formula (2) wherein each R is independently H or alkyl (1-6C).

In one group of these compounds, L is a flexible conjugating or nonconjugating linker. In this group, when  $Z$  is NR,  $Ar^2$  is preferably a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is

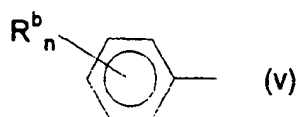


wherein  $R^b$  is a noninterfering substituent and  $n$  is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or the dotted line represents a  $\pi$  bond.

In these embodiments as well as in alternative embodiments of  $Ar^2$ , it is preferred that each  $R^b$  is independently halo, OR, SR,  $NR_2$ , NO,  $NO_2$ ,  $OCF_3$  or  $CF_3$  wherein R is H or alkyl (1-6C), or  $R^b$  comprises an aromatic system.

Preferred compounds in this group are 59-0100, 59-103, 59-104, 59-105 and  
5 59-106 (See Figure 13).

In another group of these compounds with flexible linkers, Z is S, and  $Ar^2$  is preferably a substituted or unsubstituted aromatic system containing a 6-membered heterocycle or is of the formula



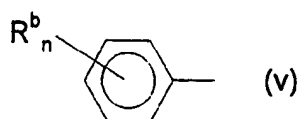
10 wherein  $R^b$  is a noninterfering substituent and n is an integer of 0-5; and/or L is  $-N=N-$ ,  $-N=CR-$ ,  $-RC=CR-$ ,  $-NRNR-$ ,  $-CR_2NR-$ ,  $-CR_2CR_2-$ ,  $-NRCO-$  or  $-CONR-$  where R is H or alkyl (1-6C); and/or the dotted line represents a  $\pi$  bond.

In such compounds, regardless of the choice of  $Ar^2$ , preferred are those compounds wherein each  $R^b$  is independently halo, OR, SR,  $NR_2$ , NO,  $NO_2$ ,  $OCF_3$  or  
15  $CF_3$  wherein R is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system.

Both when Z is S and when Z is NR, it is preferred that m is 0 and/or each  $R^b$  is independently OR, SR or halo, where  $n=2$  and at least one  $R^b$  is independently OR or SR and/or L is  $-NHCO-$  or  $-CR=CR-$ .

Preferred compounds in this group include compounds 59-002, 59-0070,  
20 59-0072, 59-0099, 59-0102, the benzothiazole counterpart of 59-0104, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195, 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210, especially the benzothiazole counterpart of 59-0104 or compounds 59-0147, 59-0205 or 59-0210. (See Figure 13)

25 Z can also be CR,  $CR_2$  or O; here it is also preferred that  $Ar^2$  is

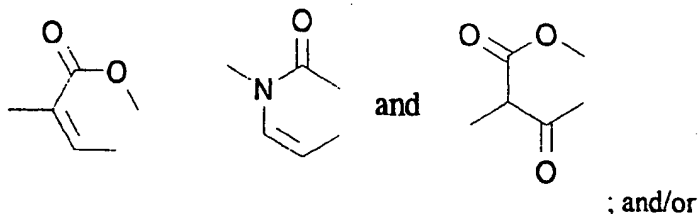


wherein  $R^b$  is a noninterfering substituent and  $n$  is an integer of 0-5, and/or  $L$  is  $-N=N-$ ,  $-N=CR-$ ,  $-RC=CR-$ ,  $-NRNR-$ ,  $-CR_2NR-$ ,  $-CR_2CR_2-$ ,  $-NRCO-$  or  $-CONR-$  where  $R$  is H or alkyl (1-6C), and/or the dotted line represents a  $\pi$  bond.

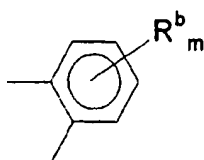
- 5 In these compounds, too, it is preferred that each  $R^b$  is independently halo, OR, SR,  $NR_2$ , NO,  $NO_2$ ,  $OCF_3$  or  $CF_3$  wherein  $R$  is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system. A preferred compound is 896-5005. (See Figure 4)

The compounds wherein  $Ar^1$  is 1a or 2a as above may also contain a constrained linker.

- 10 In these compounds, preferred  $Z$  is S or  $NR$ ; and/or those wherein  $L$  is selected from the group consisting of



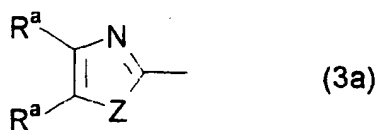
$Ar^2$  is



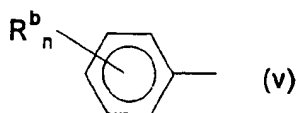
- 15 wherein  $R^b$  is a noninterfering substituent and  $m$  is 0-4.

Preferably, each  $R^b$  is independently halo, OR, SR,  $NR_2$ , NO,  $NO_2$ ,  $OCF_3$  or  $CF_3$  wherein  $R$  is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system. A preferred compound is 59-0124. (See Figure 13)

In another group of preferred embodiments,  $Ar^1$  is of the formula



wherein each  $R^a$  is independently a noninterfering substituent or is H and Z is NR, S or O, wherein R is alkyl (1-6C) or H, especially where Z is S and/or wherein  $Ar^2$  is

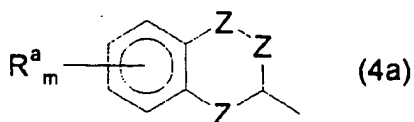


5

wherein  $R^b$  is a noninterfering substituent and n is an integer of 0-5,; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCO- or -CONR- where R is H or alkyl (1-6C), and/or the dotted line represents a  $\pi$  bond. Especially preferred are those compounds where each  $R^b$  is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system.

10

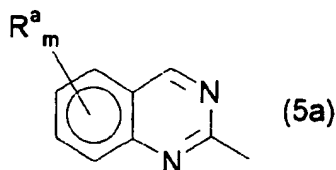
In another group of compounds,  $Ar^1$  is



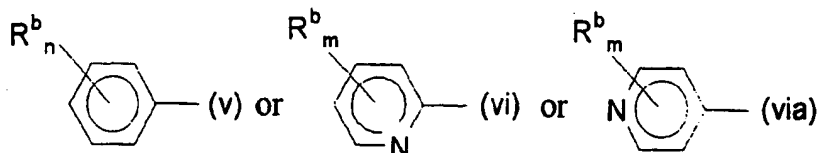
wherein  $R^a$  is a noninterfering substituent, m is an integer of 0-4, each dotted line represents an optional  $\pi$ -bond, each Z is independently N, NR, CR or CR<sub>2</sub>, where each R is independently H or alkyl (1-6C) with the proviso that at least one Z is N or NR.

15

Particularly preferred members of this group are those wherein  $Ar^1$  is



especially those wherein  $Ar_2$  is

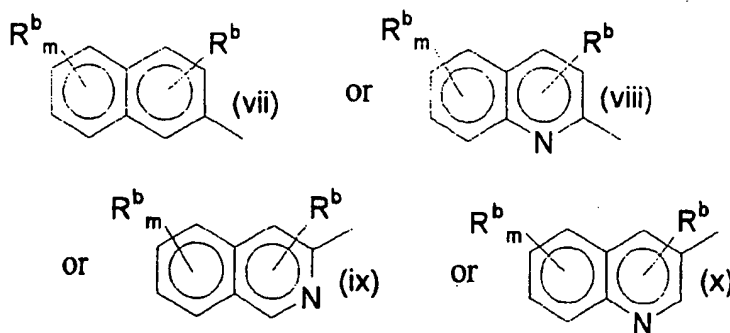


wherein each  $R^b$  is independently a noninterfering substituent, and  $n$  is 0-5 and  $m$  is 0-4, and/or  $L$  is  $-N=N-$ ,  $-RC=CR-$ ,  $-RC=N-$ ,  $-NRCO-$ ,  $-NRCR_2-$ ,  $-NRCR_2CR_2-$ ,  
 5  $-NRCR_2CO-$ ,  $-NRNR-$ ,  $-CR_2CR_2-$ ,  $-NRCR_2CR_2NR-$ ,  $-NRCR=CRNR-$  or  $-NRCOCR_2NR-$ .

In general, preferably each  $R^b$  is independently halo, OR, SR,  $NR_2$ , NO,  $NO_2$ ,  $OCF_3$  or  $CF_3$  wherein  $R$  is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system.

In an especially preferred group,  $m$  is 0, each  $R^b$  is  $NR_2$  or OR and  $n$  is 1 or 2,  
 10 and/or  $L$  is  $-CR=CR-$ ,  $-N=N-$  or  $-NRCO-$ , especially the compounds of formulas 59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 50-0197, 59-0198, 59-0199 or 59-0480. (See Figure 13)

Also preferred are those wherein  $Ar^1$  has formula (4a) or (5a) and wherein  $Ar_2$  is substituted or unsubstituted quinolyl or naphthyl of the formula



15

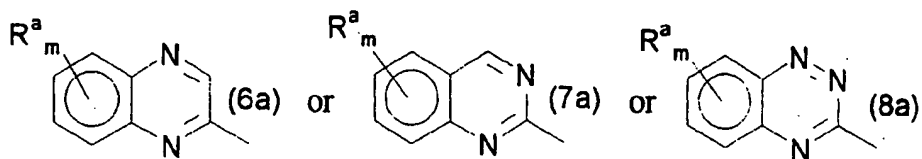
wherein each  $R^b$  is a noninterfering substituent and  $m$  is 0-4.

Preferred among these are those wherein  $L$  is  $-N=N-$ ,  $-RC=CR-$ ,  $-RC=N-$ ,  
 $-NRCO-$ ,  $-NRCR_2-$ ,  $-NRCR_2CR_2-$ ,  $-NRCR_2CO-$ ,  $-NRNR-$ ,  $-CR_2CR_2-$ ,  
 $-NRCR_2CR_2NR-$ ,  $-NRCR=CRNR-$  or  $-NRCOCR_2NR-$ , and/or wherein each  $R^b$  is  
 20 independently halo, OR, SR,  $NR_2$ , NO,  $NO_2$ ,  $OCF_3$  or  $CF_3$  wherein  $R$  is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system and  $m$  is 0, 1 or 2.

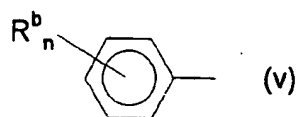


The compounds 59-0089, 59-0090, 59-0092 or 59-0094 are particularly preferred.

$Ar^1$  is also preferably



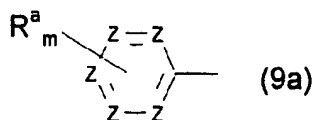
- 5 wherein each  $R^a$  is a noninterfering substituent and  $m$  is 0-4, in particular where  $L$  is  $-N=N-$ ,  $-RC=CR-$ ,  $-RC=N-$ ,  $-NRCO-$ ,  $-NRCR_2-$ ,  $-NRCR_2CR_2-$ ,  $-NRCR_2CO-$ ,  $-NRNR-$ ,  $-CR_2CR_2-$ ,  $-NRCR_2CR_2NR-$ ,  $-NRCR=CRNR-$  or  $-NRCOCR_2NR-$ , and/or  $Ar^2$  is



- 10 wherein  $R^b$  is a noninterfering substituent and  $n$  is an integer of 0-5. Especially preferred are compounds wherein each  $R^b$  is independently halo, OR, SR,  $NR_2$ , NO,  $NO_2$ ,  $OCF_3$  or  $CF_3$  wherein  $R$  is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system, in particular compounds 59-203, 59-285 or 59-286. (See Figure 13)

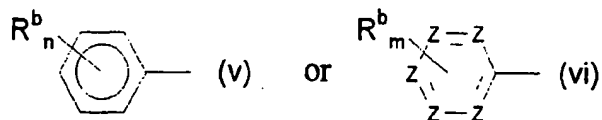
When  $Ar^1$  is of formula (4a),  $L$  can also be a constrained linker.

- 15 In still another preferred set,  $Ar^1$  is



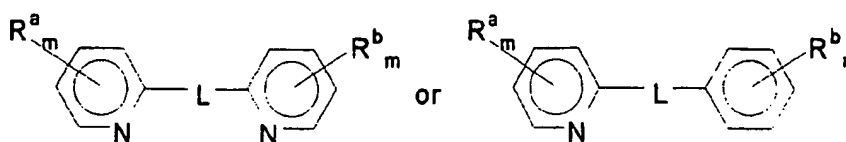
wherein each  $R^a$  is independently a noninterfering substituent,  $m$  is an integer of 0-4, each  $Z$  is independently N or CR, where  $R$  is H or alkyl (1-6C), with the proviso that at least one  $Z$  must be N and at least one  $Z$  must be CR.

- 20 In these compounds,  $L$  is preferably a flexible conjugating or nonconjugating linker, and/or wherein  $Ar^2$  is



wherein each  $R^b$  is independently a noninterfering substituent, and in (vi) each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

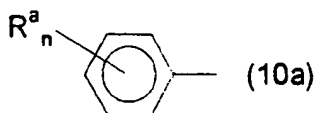
5 Preferred such compounds have the formula



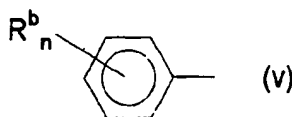
Preferred L embodiments in this group include -N=N-, -RC=CR-, -RC=N-,  
 -NRCO-, -NRCR<sub>2</sub>-, -NRCR<sub>2</sub>CR<sub>2</sub>-, -NRCR<sub>2</sub>CO-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-,  
 -NRCR<sub>2</sub>CR<sub>2</sub>NR-, -NRCR=CRNR- or -NRCOCR<sub>2</sub>NR-; preferred for  $R^a$  and  $R^b$  are  
 10 halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $R^a$  or  $R^b$   
 comprise aromatic systems and each m and n is independently 0, 1 or 2.

In particular, compounds are preferred where L is -NHCR<sub>2</sub>CR<sub>2</sub>NH- and  $R^a$  is  
 CF<sub>3</sub> para to L, especially compounds 59-0145, 59-0450, 59-0459 or 59-0483. (See  
 Figure 13)

15 Finally, in another preferred group,  $Ar^1$  is



wherein each  $R^a$  is a noninterfering substituent, and n is an integer of 0 and 5,  
 and wherein L is a flexible linker that contains at least one nitrogen. In the alternative  
 or in addition,  $Ar^2$  is of the formula



and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR<sub>2</sub>-, -NRCR<sub>2</sub>CR<sub>2</sub>-,  
 -NRCR<sub>2</sub>CO-, -NRNR<sub>2</sub>CR<sub>2</sub>CR<sub>2</sub>-, -NRNR<sub>2</sub>CR=CR-, -NRNR<sub>2</sub>COCR<sub>2</sub>-,  
 -NRNR<sub>2</sub>COCR=CR-, -NRNR<sub>2</sub>CS<sub>2</sub>CR<sub>2</sub>-, -NRNR<sub>2</sub>CS<sub>2</sub>CR=CR-, -NRNR<sub>2</sub>CONR-,  
 -NRNR<sub>2</sub>CSNR-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NR<sub>2</sub>CR<sub>2</sub>CR<sub>2</sub>NR-, -NR<sub>2</sub>CR=CRNR- or  
 5 -NR<sub>2</sub>COCR<sub>2</sub>NR-. It is preferred that each R<sup>b</sup> is independently halo, OR, SR, NR<sub>2</sub>, NO,  
 NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or R<sup>b</sup> comprises an aromatic system.

Especially preferred are those compounds wherein L is -CR=CRCONRNR-,  
 -CR=CRCSNRNR-, -CR<sub>2</sub>CONRNR-, -CR<sub>2</sub>CSNRNR-, -NRNR<sub>2</sub>CONR- or  
 -NRNR<sub>2</sub>CSNR- and/or R<sup>b</sup> is -NR<sub>2</sub> and n=1 wherein R<sup>b</sup> is in the para position, especially  
 10 wherein R<sup>a</sup> is -COOR and m is 1; most especially compounds 59-0045, 59-0095,  
 59-0096, 59-0097 and 59-0098. (See Figure 13)

As set forth above, several families of preferred embodiments are defined by  
 specifying Ar<sup>1</sup> and Ar<sup>2</sup>, and L. In one such family, wherein Ar<sup>1</sup> is an aromatic system  
 containing a 5-membered heterocyclic ring, the compound 59-0072, wherein Ar<sup>1</sup> is  
 15 unsubstituted benzothiazole, the linker (Ar<sup>1</sup> → Ar<sup>2</sup>) is NHCO, and Ar<sup>2</sup> is 2-methoxy-4-  
 methylthiophenyl was used as a lead compound and variations of the structure studied.  
 Figure 5 shows representative compounds synthesized to analyze the effects of the  
 nature of the linker, various alternatives of Ar<sup>1</sup> wherein Z is O, NR or S, and the effect  
 of substitution on the phenyl moiety, as well as the heterocycle.

20 Figure 5 gives the structures of these compounds, along with their maximum  
 activity as compared to 59-0008 at 10 μM (the maximum for 59-0008) in the *in vitro*  
 bone growth stimulation assay as well as the concentration at which 50% of maximum  
 stimulation of the BMP promoter was obtained (EC<sub>50</sub>). See Example 1 for the details  
 of this assay. The results of this study indicate that the amide linker in 59-0072 can  
 25 readily be substituted by -CH=CH- and that the substitution on the phenyl ring had  
 advantageous effects in the order: 2-Cl-4-OMe=2,4-di-OMe=2-OMe-4-SMe  
 >>3,4-di-OMe=4-OMe. In general, compounds 59-0205, 59-0104, 59-0107, 59-0210  
 and 59-0124 have the best activity in the primary screen, but only 59-0124 is active in  
 the *ex vivo* calvarial assay described in Example 3.

Similar structure/activity relationship studies were conducted for compounds wherein Ar<sup>1</sup> is quinoline. In this study, compound 50-0197, wherein Ar<sup>1</sup> is unsubstituted quinoline, the linker is -CH=CH-, and Ar<sup>2</sup> is p-dimethylaminophenyl was used as a lead compound. The compounds synthesized in this study are shown in Figure 6, along with their maximum stimulation characteristics and EC<sub>50</sub> in the assay of Example 1. The results of these studies showed that quinoxaline analogs are the most active in the assay, followed by quinoline; the linker can most preferably be -CH=CH- or -N=N- as judged by activity in the assay, but -CH=CH- is preferred *in vivo* due to its lack of toxicity. Preferred substituents on the phenyl ring in Ar<sup>2</sup> include 2,4-di-OMe; 4-NMe<sub>2</sub>-2-OMe, and 4-NMe<sub>2</sub>. For the compounds in Figure 6, 59-0282 and 50-0197 were moderately active and 59-0203 was highly active in the *ex vivo* calvarial assay described hereinabove as a modification of Gowen, M. and Mundy, G. *J Immunol* (1986) 136:2478-2482.

Another group of compounds wherein Ar<sup>1</sup> and Ar<sup>2</sup> are pyridyl heterocycles was also studied. In this case, compound 59-0145 was used as the lead compound; the linker, the nature of the substituents R<sup>a</sup> and R<sup>b</sup> were varied. In one instance, a quinolyl residue was substituted for a pyrimidine residue as Ar<sup>2</sup>. Representative compounds used in this study are shown in Figure 7, along with the data from the screening assay.

Using 59-0145 as a lead, a CF<sub>3</sub> group in one of Ar<sup>1</sup> and Ar<sup>2</sup> appeared essential; however, one of R<sup>a</sup> or R<sup>b</sup> could also be NO<sub>2</sub> or CN. The most preferred linker is -NHCH<sub>2</sub>CH<sub>2</sub>NH-; substitution on the amino groups in L by an alkyl group appeared to reduce activity. Enhanced chain lengths also led to loss of activity.

Preferred compounds in this group, which perform better than 59-0008 in the screening assay, included 59-0450, 59-0459, 59-0480, and 59-0483.

Finally, a series in which Ar<sup>1</sup> is 3-carboxyphenyl was studied using 59-0045 as the lead compound. In 59-0045, L is -NHN=CH- and Ar<sup>2</sup> is p-dimethylaminophenyl. Figure 8 shows the compounds synthesized in this series. Under the circumstances of this assay, analogs wherein R<sup>b</sup> was, instead of a nitrogen-containing moiety, F, Cl, or OMe were inactive. Preferred compounds in this series are 59-0096 and 59-0098. 59-0098 is very active in the *ex vivo* calvarial assay described above.

### Synthesis of the Compounds Useful in the Invention

Many of the compounds useful in the invention are commercially available and can be synthesized by art-known methods. Those compounds useful in the invention which are new compounds, can similarly be obtained by methods generally known in the art, as described in the Examples below.

The following examples are intended to illustrate, but not to limit, the invention.

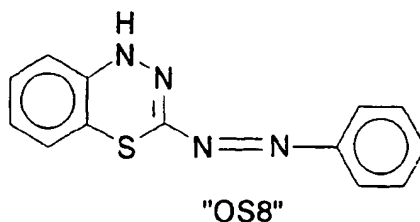
10

#### Preparation A

Compound 59-0008 used as a standard in the assays, was synthesized according to the procedure of McDonald, W. S., *et al. Chem Comm* (1969) 392-393; Irving, H. N. N. H. *et al. Anal Chim Acta* (1970) 49:261-266. Briefly, 10.0 g of dithizone was taken up in 100 ml EtOH and 50 ml AcOH and heated at reflux for 18 h. After cooling, this was diluted first with 100 ml water and then with 50 ml 1N NaOH. This was then further neutralized by the addition of 6 N NaOH to bring the pH to 5.0. This deep purple mixture was then concentrated on a rotavapor to remove organics. Once the liquid had lost all of its purple color, this was filtered to collect the dark precipitate. Purification by flash chromatography (4.5 x 25.7 cm; EtAc/Hep. (1:4); R<sub>f</sub> 0.22) followed by recrystallization from EtOH gave 2.15 g (25% yield) of dark purple crystals, mp=184-185 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.90 (d of d, J<sub>1</sub>=7.7, J<sub>2</sub>=2.2, 2H), 7.64 (hump, 1H), 7.49 (m, 3H), 7.02 (m, 1H), 6.91 (m, 2H), 6.55 (d, J=8.1, 1H). MS (EI) 254 (47, M<sup>+</sup>), 105 (26), 77 [100], 51 (27). HRMS (EI, M<sup>+</sup>) 254.0626 (calcd 254.0626182). Anal. Calcd for C<sub>13</sub>H<sub>10</sub>N<sub>4</sub>S: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.40; H, 4.20; N, 22.06.

Example 1High Throughput Screening

Several tens of thousands of compounds were tested in the assay system set forth in WO 96/38590, published 5 December 1996, and incorporated herein by  
5 reference. The standard positive control was 59-0008 (also denoted "OS8"), which is of the formula:



In more detail, the 2T3-BMP-2-LUC cells, a stably transformed osteoblast cell line described in Ghosh-Choudhury *et al. Endocrinology* (1996) 137:331-39,  
10 referenced above, was employed. The cells were cultured using  $\alpha$ -MEM, 10% FCS with 1% penicillin/streptomycin and 1% glutamine ("plating medium"), and were split 1:5 once per week. For the assay, the cells were resuspended in a plating medium containing 4% FCS, plated in microtiter plates at a concentration of  $5 \times 10^3$  cells (in 50  $\mu$ l)/well, and incubated for 24 hours at 37°C in 5% CO<sub>2</sub>. To initiate the assay, 50  $\mu$ l of  
15 the test compound or the control in DMSO was added at 2X concentration to each well, so that the final volume was 100  $\mu$ l. The final serum concentration was 2% FCS, and the final DMSO concentration was 1%. Compound 59-0008 (10  $\mu$ M) was used as a positive control.

The treated cells were incubated for 24 hours at 37°C and 5% CO<sub>2</sub>. The  
20 medium was then removed, and the cells were rinsed three times with PBS. After removal of excess PBS, 25  $\mu$ l of 1X cell culture lysing reagent (Promega #E153A) was added to each well and incubated for at least ten minutes. Optionally, the plates/samples could be frozen at this point. To each well was added 50  $\mu$ l of luciferase substrate (Promega #E152A; 10 ml Promega luciferase assay buffer per 7  
25 mg Promega luciferase assay substrate). Luminescence was measured on an

automated 96-well luminometer, and was expressed as either picograms of luciferase activity per well or as picograms of luciferase activity per microgram of protein.

In this assay, compound 59-0008 (3-phenylazo-1H-4,1,2-benzothiadiazine) exhibited a pattern of reactivity, as shown in Figure 2. The activity for compound 59-0008 was maximal at a concentration of approximately 3-10  $\mu$ M and, more particularly, at about 3  $\mu$ M, and thus provided a response of approximately 175 light emission units. Accordingly, other tested compounds were evaluated at various concentrations, and these results were compared to the results obtained for 59-0008 at 10  $\mu$ M (which value was normalized to 100). For instance, any tested compound in Figure 3 and Figure 4 that showed greater activity than 10  $\mu$ M of 59-0008 would result in a value over 100.

As shown in Figure 3 (46 sheets) and Figure 4 (28 sheets), several compounds were found to be particularly effective.

15

### Example 2

#### *In vivo* Calvarial Bone Growth Data

Compound 59-0008 was assayed *in vivo* according to the procedure described previously (see "*In vivo* Assay of Effects of Compounds on Murine Calvarial Bone Growth", *supra*). As compared to a vehicle control, compound 59-0008 induced a 4-fold increase in width of new calvarial bone.

In another experiment, 5 week old Swiss white mice were injected 3 times a day for 5 days over the calvaria with compound 59-0203 using PBS, 5% DMSO and 0.1% BSA as carrier. The drug was tested at 6 different doses, from 0.1-50 mg/kg/day. Animals were sacrificed 3 weeks after the injections started and calvariae were fixed, decalcified, and processed for histology. Bone histomorphometry measuring total bone area (BA/TV) confirms that FGF, used in every experiment as a positive control, shows an increase in the total bone area with all doses tested, but this increase is only significantly different from control at 1 and 5 mg/kg/day. The invention compound 59-0203 shows consistent increases over the 0.1-50 mg/kg/day range at a somewhat lower level than that obtained with FGF.

Similar results are obtained when new bone width in microns is measured. There was no new bone present in the control group. 59-0203 caused new bone formation at all doses, with a significant increase at 25-50 mg/kg/day. New bone as percentage of the total bone area was about 45% for the FGF positive control and  
5 from about 15% to 30% over the range of 0.1-50 mg/kg/day for 59-0203. There was no new bone present in the negative control.

### Example 3

#### Ex vivo Calvarial Bone Growth Assay

10 A number of compounds, in particular, those studied in connection with lead compounds classified as hydrazone/hydrazides (H) exemplified by 59-0045, benzothiazoles (T) exemplified by 59-0104, bis-pyridines (P) exemplified by 59-0145, and quinolines/quinoxalines (Q) exemplified by 59-0197, were tested in the *ex vivo* calvarial assay described hereinabove. The results of this assay are shown in Figure 9.  
15 In this assay, histomorphometry and osteoblast numbers are measured and effects are measured on an arbitrary scale from 1-3: i.e., 1, 1+, 2-, 2, 2+, 3-, 3, wherein 1 denotes "inactive." In this assay, for example, FGF scores 2-3.

The scores are assigned to bone formation on the ectocranial periosteal surface. The area immediately surrounding midline suture is excluded from analysis.

20

#### Score

- 0 Toxicity. Cell necrosis, pyknotic nuclei, matrix disintegration.
- 25 1 A score of "1" is the bone forming activity seen in control cultures containing BGJb media + 0.1% bovine serum albumin. The periosteal surface is covered by one layer of osteoblasts (at about 50% of the bone surface, with the remaining 50% being covered by bone lining cells). A score of "1-" is assigned if less than 50% of  
30 the periosteal surface is covered by osteoblasts due to inhibitory activity or minor toxicity of the agents being tested. A score of "1+" is given if over 50% of the surface is covered by osteoblasts.
- 35 2 A moderate increase in bone forming activity. 20-40% of the periosteal surface is covered by up to two layers of osteoblasts. A score of "2-" is given if less than 20% of the surface is covered by



two layers and "2+" if more than 40% of the surface is covered by two layers of osteoblasts.

- 5                   3   A score of "3" is the bone forming activity seen in control cultures containing BGJb media + 0.1% BSA +10% fetal bovine serum. More than 20% of the periosteal surface is covered by three layers of osteoblasts. The cells appear plump (size can exceed 100µm<sup>2</sup>). A score of "3-" is given if less than 20% of the periosteal surface is covered by three layers of osteoblasts and or osteoblast size is less than 100µm<sup>2</sup>. A score of "3+" has never been observed.
- 10

In all samples, toxicity, ectopic new or woven bone formation associated with osteoblasts, and osteoblast size as reflections of relative activity are noted.

- The results shown in Figure 9 represent those obtained when the measurements
- 15   were made by two different groups. It is clear that a number of compounds tested have activity in this assay. From the results shown in Figure 9, 59-0073, 59-0030, 59-0070, 59-007, 59-0019, 59-0099, 59-0072 and 59-0103 show at least some indication of activity. 59-150 and 59-0104 showed activity when measured by one group but not the other; similarly, 50-0197 had this pattern. It appears that 59-0098
- 20   and 59-0203 are quite active in this assay and 59-0145 shows a consistent moderate activity.

#### Example 4

##### Stimulation of Bone Growth in Ovariectomized Rats (OVX Assay)

- 25   The compound 59-0145 was tested at various concentrations in the OVX assay conducted as described above. The increase in bone volume was measured by two different groups; one group found 5 µg/kg/day of 59-0145 gave 21% increase over control whereas the second group found a 71% increase. At 50 µg/kg/day, the first group found a 31% increase, and the second a 54% increase.

- 30   In another experiment, the lumbar vertebrae were measured and the above dosages of 59-0145 were shown to provide a beneficial effect, as shown in Figure 10.

In another experiment, 3 month old Sprague Dawley rats were ovariectomized and depleted for six weeks. At the end of the six weeks, treatment was started with subcutaneous administration of compound 59-0145. The treatment continued for 10

weeks. At the end of the 10 weeks animals were sacrificed, bones were collected for qCT measurements and histology; serum was also collected for osteocalcin determinations.

Figure 11 shows the percentage increase in trabecular bone (proximal tibia) compared to the placebo-treated group in chronic ovariectomized rats after 10 weeks of treatment. Compound 59-0145 causes significant increase in trabecular bone at doses of 50-500 µg/kg/day.

Figure 12 shows results of qCT and bone histomorphometry in proximal tibia in the first two panels, as well as serum osteocalcin levels at the time of sacrifice as a percentage increase compared to control group (OVX placebo-treated group).

#### Example 5

##### Chondrogenic Activity

Compounds 59-008, 59-0102 and 50-0197 were assayed for effects on the differentiation of cartilage cells, as compared to the action of recombinant human BMP-2. Briefly, a mouse clonal chondrogenic cell line, TMC-23, was isolated and cloned from costal cartilage of transgenic mice containing the BMP-2 gene control region driving SV-40 large T-antigen, generated as described in Ghosh-Choudhury *et al Endocrinology* 137:331-39, 1996. These cells were cultured in DMEM/10% FCS, and were shown to express T-antigen, and also to produce aggrecan (toluidine blue staining at pH 1.0) and Type-II collagen (immunostaining) by 7 days after confluence.

For measurement of alkaline phosphatase (ALP) activity, the technique of LF Bonewald *et al. J Biol Chem* (1992) 267:8943-49, was employed. Briefly, TMC-23 cells were plated in 96 well microtiter plates in DMEM containing 10% FCS at  $4 \times 10^3$  cells/well. Two days after plating, the cells were confluent and the medium was replaced with fresh medium containing 10% FCS and different concentrations of compounds or recombinant BMP-2. After an additional 2 or 5 days incubation, the plates were washed twice with PBS, and then lysing solution (0.05% Triton X-100) was added (100 µl/well). The cells were lysed by three freeze-thaw cycles of -70°C (30 min), followed by 37°C (30 min with shaking). Twenty microliters of cell lysates

were assayed with 80  $\mu$ l of 5 mM p-nitrophenol phosphate in 1.5 M 2-amino-2-methyl-propanol buffer, pH 10.3 (Sigma ALP kit, Sigma Chemical Co., St. Louis, MO) for 10 min at 37°C. The reaction was stopped by the addition of 100  $\mu$ l of 0.5 M NaOH.

The spectrophotometric absorbance at 405 nm was compared to that of p-nitrophenol standards to estimate ALP activity in the samples. The protein content of the cell  
5 lysates was determined by the Bio-Rad protein assay kit (Bio-Rad, Hercules, CA). Specific activity was calculated using these two parameters.

At day 2, compounds 59-0008 ( $10^{-9}$  M), 59-0102 ( $10^{-7}$  M) and 59-0197 ( $10^{-9}$  M) increased ALP levels approximately 3-, 2- and 2.5-fold, respectively, as compared  
10 to the vehicle control. Recombinant BMP2 at 100, 50 or 10 ng/ml induced ALP levels approximately 10-, 4- or 1.5-fold, respectively, as compared to the vehicle control.

#### Example 6

##### Synthesis of Exemplary Compounds

15 A. Compounds of the invention wherein Ar<sup>1</sup> is of formula (1a) or (2a) can be synthesized by the procedures described in Dryanska, V. and Ivanov, K. *Synthesis* (1976) 1:37-8, using the described embodiments of Ar<sup>2</sup> and the appropriate analogous heterocycle embodied in Ar<sup>1</sup> substituted for the benzothiazole shown. Alternates to the olefin linker described can also be prepared using standard methods.

20 Compounds of the invention represented by exemplary Compound 59-0234, wherein Z is O, L is -CH=CH-, and Ar<sup>2</sup> is 2,4-dimethoxy-phenyl, including Compounds 59-0211 and 59-0233, were prepared according to the following procedure describing synthesis of Compound 59-0234. Briefly, to a N,N-dimethylformamide (DMF) solution of 2-methylbenzoxazole (1 mmol) and  
25 2,4-dimethoxybenzaldehyde (1 mmol) was added lithium t-butoxide (2 mmol). The reaction mixture was heated at 130°C for 3h. After cooling to room temperature, the reaction mix was poured into ether and washed several times with water. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to dryness. The residue was dissolved in a minimal amount of hot ether and, on standing overnight, the crystalline  
30 product was collected by filtration.

- B. Exemplary Compound 59-0150 where Ar<sup>1</sup> is of formula 4a was synthesized according to the procedure of Zamboni *et al. J Med Chem* (1992) 35:3832-44. First, 2-triphenylphosphoniumquinaldine bromide was synthesized as follows. Quinaldine (200 mmols), NBS (200 mmols) and a catalytic amount of benzoyl peroxide (10 mmols) were dissolved in 1 L of anhydrous carbon tetrachloride, and the mixture was stirred under reflux for 72 h. The mixture was cooled to RT and washed with water. The organic layer was drawn off, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a dark oil. The crude mixture was dissolved in 500 ml of acetonitrile, then triphenylphosphine (200 mmols) was added and the mixture was refluxed under nitrogen overnight. It was then cooled to RT and diluted with anhydrous ether. The precipitated solid was collected by filtration, washed thoroughly with anhydrous ether and dried in vacuo overnight, yielding 25 g of a tan crystalline solid which showed a single spot by TLC (silica gel, 5 % MeOH in DCM).
- A Wittig reaction was then performed. Briefly, under anhydrous conditions, 0.738 g (1.68 mmol) 2-triphenylphosphoniumquinaldine bromide in dry THF was cooled to -78°C. 1.0 ml (2.5 mmol, 2.5 M in hexanes) n-butyl lithium was slowly added, and this was allowed to react for 20 min. 0.301 g (1.68 mmol) 4-(N,N-dimethylamino)-2-methoxybenzaldehyde was then added. After a few minutes, the cold bath was removed, and this was left at ambient temp. for 18 h. The reaction was quenched by the addition of aq. sat. NH<sub>4</sub>Cl. This was extracted with EtAc, and the organics washed with additional NH<sub>4</sub>Cl, sat. NaHCO<sub>3</sub>, and sat. NaCl. This was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent stripped on a rotavapor. After flash chromatography (3.8 x 18.0 cm; EtAc/Hep. (1:3); R<sub>f</sub> 0.29), 0.135 g (26% yield) of a red solid was obtained, mp=185-187 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.04 (t, J=9.0, 2H), 7.94 (d, J=16.5, 1H), 7.74 (d, J=8.1, 1H), 7.73 (d, J=8.5, 1H), 7.66 (t of d, J<sub>t</sub>=7.6, J<sub>d</sub>=1.4, 1H), 7.61 (d, J=8.8, 1H), 7.43 (t of d, J<sub>t</sub>=7.6, J<sub>d</sub>=1.1, 1H), 7.29 (d, J=16.6, 1H), 6.37 (d of d, J<sub>1</sub>=8.7, J<sub>2</sub>=2.4, 1H), 6.22 (d, J=2.4, 1H), 3.93 (s, 3H), 3.03 (s, 6H).. Anal. Calcd for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O: C, 78.92; H, 6.62; N, 9.20. Found:

C. Exemplary Compound 59-0209 was synthesized according to the procedure of McOmie, J. F. W.; and West, D. E., *Org Synth, Collect Vol V* (1973) 412. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr<sub>3</sub> in dry CH<sub>2</sub>Cl<sub>2</sub> at -78°C. After 15 min, this was  
5 allowed to warm to RT. After 2 h, the reaction was re-cooled to -78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 ml MeOH. After 10 min, this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurred in MeOH and re-stripped. Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); R<sub>f</sub> 0.25) gave  
10 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for C<sub>17</sub>H<sub>13</sub>NO: C, 82.57; H, 5.30; N, 5.66. Found:

15 D. Exemplary Compound 59-0019 was synthesized as follows: to a xylene solution of 2-methylquinoxaline (10 mmol) and 4-dimethylaminobenzaldehyde (10 mmol) was added piperidine (2 ml). The solution was heated at reflux for 1 day, at which time DBU (200 µL) was added and reflux continued for another 2 days. The solution was cooled to RT and extracted with 1 M citric acid. The aqueous phase was  
20 repeatedly extracted with ether. The organic phases were pooled, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness. The residue was chromatographed on silica gel. The product was eluted using 8:1:1 dichloromethane:ether: hexane. Fractions containing pure product were pooled and evaporated to dryness. The residue was triturated with ether and filtered to give the desired compound.

25 E. Exemplary Compound 59-0183 and related Compound 59-0182 were synthesized according to the following procedure. Briefly, quinaldic acid (0.5 mmol) and HATU (0.5 mmol) were dissolved in 2.5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (1 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min.  
30 The appropriate amine (0.5 mmol) was then added all at once to the above stirred

mixture, and the mixture was stirred overnight at RT. It was then diluted with 25 mL of cold water with vigorous stirring, the precipitate was collected by filtration and washed thoroughly with water several times, and then dried *in vacuo* overnight. The product was purified by flash column chromatography over silica gel eluting with  
5 dichloromethane. The pure product was obtained as a tan powder.

F. Exemplary Compound 59-0209 was synthesized according to the following procedure. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr<sub>3</sub> in dry CH<sub>2</sub>Cl<sub>2</sub> at -78°C. After 15 min, this was allowed to warm to RT. After 2 h, the reaction was re-cooled to -  
10 78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 ml MeOH. After 10 min, this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurried in MeOH and re-stripped. Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); R<sub>f</sub> 0.25) gave 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). <sup>1</sup>H  
15 NMR (DMSO-d<sub>6</sub>) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for C<sub>17</sub>H<sub>13</sub>NO: C, 82.57; H, 5.30; N, 5.66. Found:

G. Other embodiments wherein AR<sup>1</sup> is of formula (4a) can be synthesized  
20 as follows:

a. Quinoline azo compounds (59-0030 and 59-0078) may be prepared by reaction of 2-aminoquinoline with a nitrosobenzene (Brown, E. V., *et al*, *J Org Chem* (1961) 26:2831-33; Brown, E. V; \_\_\_\_\_ (1969) 6:571-73).

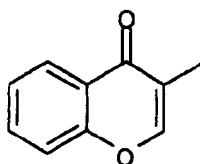
25 b. Azo derivatives may be obtained by reaction of 2-aminoquinolines with aldehydes, Morimoto, T., *et al.*, *Chem Pharm Bull* (1977) 25:1607-09; Renault, J., *et al.*, *Hebd Seances Acad Sci, Ser C* (1975) 280:1041-43; and Lugovkin, B. P.; *Zh Obshch Khim* (1972) 42:966-69.

c. Imino derivatives may be obtained by reaction of 2-formylquinolines with anilines, Tran Quoc Son, *et al.*, (1983) 21:22-26; Hagen,  
30

V. *et al. Pharmazie* (1983) 38:437-39; and Gershuns, A. L., *et al., Tr Kom Anal Khim, Akad Nauk SSSR* (1969) 17:242-50.

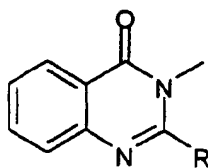
5 d. Alternatively conjugated linkers can be formed by bromination of the olefin of 50-0197 with Br<sub>2</sub> in AcOH followed by elimination with DBU as set forth in Zamboni *et al. J Med Chem* (1992) 35:3832-44.

H. Analogs having the constrained linker depicted below:



may be synthesized by reference to the methods described in Gorbulenko, N.V.  
10 *et al. Dokl Akad Nauk Ukr SSR* (1991) 5:117-23, substituting the 6-membered heterocycle for benzothiazole.

Related, compounds having the constrained linker depicted below:



R = alkyl, OH

15 may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. *Acta Cienc Indica Chem* (1992) 18:419-22; Kandeel, Maymona M., in *Phosphorus, Sulfur, Silicon, Relat Elem* (1990) 48:149-55; Salem, M.A. & Soliman, E.A. *Egypt J Chem* (1985) 27:779-87; Garin, J. *et al. Synthesis* (1984) 6:520-22, and Ayyangar N. R. *et al. Dyes and Pigments* (1990)  
20 13:301-10.

I. Exemplary Compound 59-0145 can be synthesized according to the following method. Briefly, a mixture of 2-chloro-5-trifluoromethylpyridine (15 mmol), ethylenediamine (6 mmol), and diisopropylethylamine (18 mmol) was heated at reflux for 18 h. After cooling to room temperature, the solid mass was triturated with

dichloromethane. The product was filtered and then suspended in hot EtOAc:CHCl<sub>3</sub> (50:50, 800 mL) and filtered to remove insoluble material. The volume was reduced to ~200 mL by heating on a steam bath. On standing, crystals of pure product were deposited.

- 5           Related compounds may be synthesized by reference to the method described for Compound 59-0145, and by reference to the methods described in the following publications: Tzikas, A. & Carisch, C., US Patent No. 5,393,306, issued February 28, 1995; Herzig, P. & Andreoli, A., EP 580554, published January 26, 1994; Pohlke, R. & Fischer, W., DE 3938561, published May 23, 1991. Analogs containing the structure
- 10   O-(CH<sub>2</sub>)<sub>n</sub>-O may be synthesized by reference to the previous citations, as well as the following publications: Kawato, T. & Newkome, G. *Heterocycles* (1990) 31:1097-104; Kameko, C. & Momose, Y. *Synthesis* (1982) 6:465-66; Tomlin, C.D.S. *et al.*, GB 1161492, published August 13, 1969.

- J.       Exemplary Compound 59-0097 and exemplary Compound 59-0201
- 15   were synthesized according to the following general procedure. Briefly, the isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was
- 20   then diluted with 50 mL of cold water with vigorous stirring. The precipitate was collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder. The compounds of the invention are produced by
- 25   substituting for at least one phenyl group the appropriate heterocycle.

- K.       Compounds of the class represented by exemplary Compound 59-0045 can be synthesized using standard procedures for the synthesis of phenyl hydrazones of aromatic aldehydes, as described in any organic textbook. The synthesis of exemplary Compound 59-0045 may be performed as follows. Briefly, a suspension of 3-
- 30   hydrazinobenzoic acid (1 mmol), p-dimethylaminobenzaldehyde (1 mmol), and AcOH



(50  $\mu$ L) in EtOH:H<sub>2</sub>O (4 mL:1 mL) was heated at 105°C in a sealed vial for 3 h. After cooling, a bright yellow solid was removed by filtration. The solid was washed with cold MeOH and then with ether to give pure product.

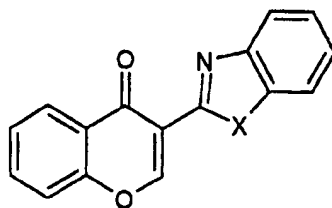
L. Exemplary Compound 59-0096 and related, exemplary Compounds 59-0098, 59-0095, 59-0107, 59-0108, 59-0109, 59-0110 and 59-0200 may be synthesized according to the following general procedure. Briefly, the appropriate carboxylic acid (1 mmol) and HATU ([O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate]; 1 mmol) were dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethylamine (3 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min. 3-Hydrazinobenzoic acid (1 mmol) was then added all at once to the above stirred mixture and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring and the precipitate was collected by filtration and washed thoroughly with water several times and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 - 10 % methanol in dichloromethane. The pure product was obtained as a tan crystalline solid.

M. Exemplary Compound 59-0097 and exemplary Compound 59-0201 were synthesized according to the following general procedure. Briefly, the isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethylamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring. The precipitate was collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder.

N. Exemplary Compound 59-0125 where R<sup>1</sup> is methoxy, m is 1, the linker is azo and Ar<sup>2</sup> is di(2-hydroxyethyl) amino, and related compounds having an azo

linker can be prepared in a manner similar to that described by Alberti, G. *et al. Chim Ind (Milan)* (1974) 56:495-97.

O. Exemplary Compound 59-0124 and related, constrained analogs having the structure depicted below:

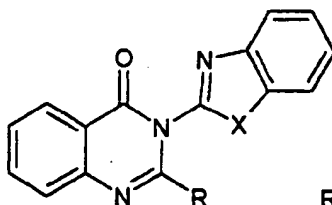


5

may be synthesized by reference to the methods described in Gorbulenko, N.V. *et al. Dokl Akad Nauk Ukr SSR* (1991) 5:117-23.

Related, constrained analogs having the structure depicted below:

10



R= alkyl, OH

may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. *Acta Cienc Indica Chem* (1992) 18:419-22; Kandeel, Maymona M., in *Phosphorus, Sulfur, Silicon, Relat Elem* (1990) 48:149-55; Salem, M.A. & Soliman, E.A. *Egypt J Chem* (1985) 27:779-87; Garin, J. *et al. Synthesis* (1984) 6:520-22, or according to the representative procedure described in Ayyangar N. R. *et al. Dyes and Pigments* (1990) 13:301-10.

Claims

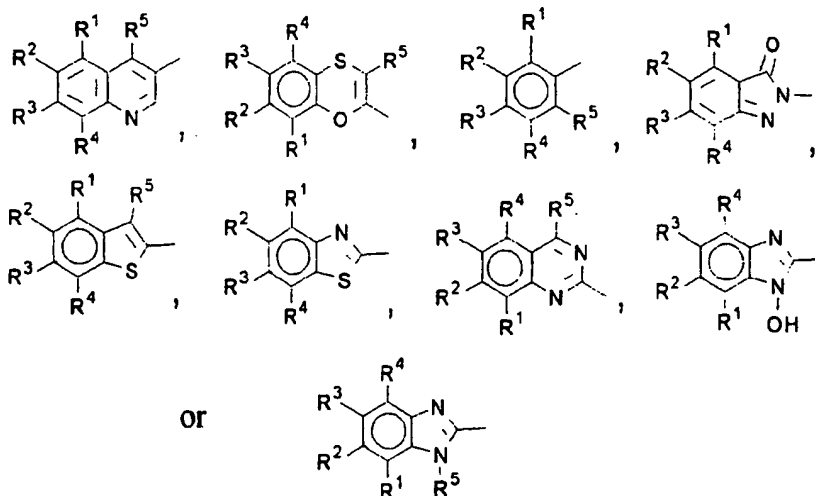
1. A method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth or replacement and/or an undesirable level of bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of a compound of the formula:



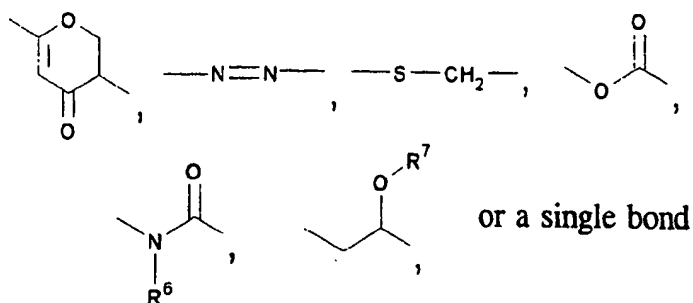
- wherein each of  $\text{Ar}^1$  and  $\text{Ar}^2$  is independently a substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted aromatic system containing a 6-membered heterocycle or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and

L is a linker which spaces  $\text{Ar}^1$  from  $\text{Ar}^2$  at a distance of 1.5Å-15Å.

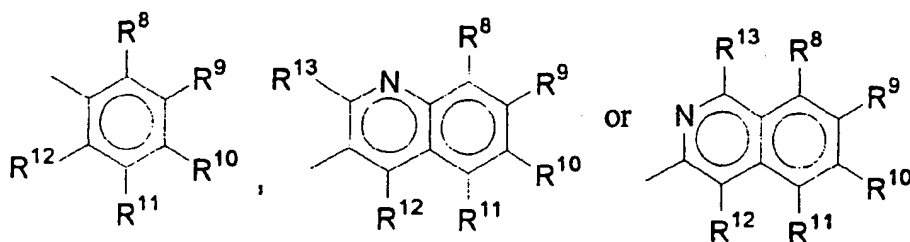
2. The method of claim 1 with the proviso that in the compound of formula (1), if  $\text{Ar}^1$  is



and L is



Ar<sup>2</sup> cannot be



wherein

5 R<sup>1</sup> is selected from the group consisting of:

H, OH, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 alkylthio, halo and (C1-C12)alkyl-carbonyloxy;

R<sup>2</sup> is selected from the group consisting of:

10 H, OH, halo, C1-C6 alkyl, C1-C6 alkenyl, C1-C6 alkoxy and (C1-C12)alkyl-carbonyloxy;

R<sup>3</sup> is selected from the group consisting of:

H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkenyl and (C1-C12)alkyl-carbonyloxy;

R<sup>4</sup> is selected from the group consisting of:

15 H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy and (C1-C12)alkyl-carbonyloxy;

R<sup>5</sup> is selected from the group consisting of:

H, halo, C1-C6 alkyl, C1-C6 alkoxy, -OC(=O)Me, phthalimide and (C1-C12)alkyl-carbonyloxy;

R<sup>6</sup> is selected from the group consisting of:

20 H, OH, -NH<sub>2</sub>, C1-C4 alkyl and C1-C4 alkoxy;

$R^7$  is selected from the group consisting of:

H, C1-C4 alkyl, (C1-C4)alkyl-carbonyl and (C7-C10)arylalkyl;

$R^8$  is selected from the group consisting of:

H, OH, halo,  $-CF_3$ , C1-C4 haloalkyl, C1-C4 alkyl, C1-C4 alkoxy,

5  $-NHC(=O)Me$  and  $-N(C1-C4\text{ alkyl})_2$ ;

$R^9$  is selected from the group consisting of:

H, OH, halo,  $-CN$ ,  $-NO_2$ , C1-C4 haloalkyl, C1-C8 alkyl, C1-C8 alkoxy,

$-NHC(=O)Me$  and  $-OC(=O)Me$ ;

$R^{10}$  is selected from the group consisting of:

10 H, OH, halo,  $-CN$ ,  $-NO_2$ , C1-C4 haloalkyl,  $-CO_2H$ , C1-C12 alkyl, C1-C12

alkoxy, phenyl, C1-C12 alkenyl, (C1-C4)alkoxycarbonyl,  $-NHC(=O)Me$ , (C1-

C4)alkylcarbonyl, (C1-C12)alkylcarbonyloxy and heteroaryl;

$R^{11}$  is selected from the group consisting of:

H, OH, halo, C1-C4 haloalkyl,  $-CF_3$ , C1-C4 alkyl,  $-NH_2$ , C1-C4 alkoxy,

15  $-NHC(=O)Me$ , C1-C4 alkenyl, (C1-C4)alkoxycarbonyl, (C1-C4)alkylcarbonyl, and

(C1-C4)alkylcarbonyloxy;

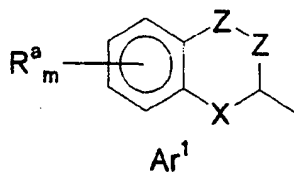
$R^{12}$  is selected from the group consisting of:

H, OH,  $-NH_2$ , C1-C4 alkyl, C1-C4 alkoxy and (C1-C4)alkylcarbonyl; and

$R^{13}$  is selected from the group consisting of:

20 H, OH, halo,  $-NH_2$ , C1-C4 alkyl, C1-C4 alkoxy  $-N(C1-C4)alkyl$ .

3. The method of claim 1 with the proviso that in the compound of formula (1), if  $Ar^1$  is



25 wherein  $R^a$  is a noninterfering substituent;

$m$  is an integer of 0-4;

each dotted line represents an optional  $\pi$ -bond;

each Z is independently N, NR, O, S, CR or CR<sub>2</sub>, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO<sub>2</sub>; and

L is a flexible linker,

- 5 then Ar<sup>2</sup> is not a substituted or unsubstituted 6-membered aromatic ring;  
if Ar<sup>1</sup> is

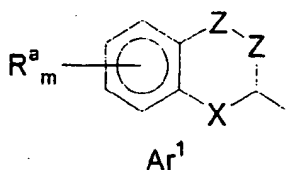


wherein R<sup>a</sup> is a noninterfering substituent;

n is an integer of 0 and 5; and

- 10 L is a flexible linker which does not contain nitrogen or is a constrained linker,  
then Ar<sup>2</sup> is not a substituted or unsubstituted phenyl or a substituted or  
unsubstituted naphthyl.

4. The method of claim 2 with the further proviso that in the compound of  
15 formula (1), if Ar<sup>1</sup> is



wherein R<sup>a</sup> is a noninterfering substituent;

m is an integer of 0-4;

each dotted line represents an optional  $\pi$ -bond;

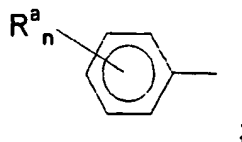
- 20 each Z is independently N, NR, O, S, CR or CR<sub>2</sub>, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO<sub>2</sub>; and

L is a flexible linker,

then Ar<sup>2</sup> is not a substituted or unsubstituted 6-membered aromatic ring;

if Ar<sup>1</sup> is

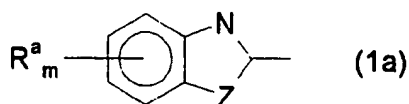


wherein R<sup>a</sup> is a noninterfering substituent;

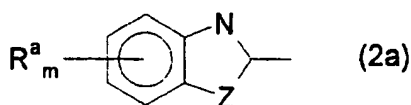
n is an integer of 0 and 5; and

- 5 L is a flexible linker which does not contain nitrogen or is a constrained linker,  
then Ar<sup>2</sup> is not a substituted or unsubstituted phenyl or a substituted or  
unsubstituted naphthyl.

5. The method of any of claims 1-4 wherein Ar<sup>1</sup> is



or



10

wherein each R<sup>a</sup> is a noninterfering substituent;

m is an integer of 0-4;

the dotted line represents an optional  $\pi$  bond;

Z is O, S, NR or CR<sub>2</sub> in formula (1) or is CR in formula (2) where each R is

- 15 independently H or alkyl (1-6C); and

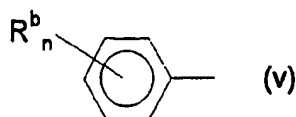
L is a flexible conjugating or nonconjugating linker or is a constrained linker.

6. The method of claim 5 wherein L is a flexible conjugating or  
nonconjugating linker.

20

7. The method of claim 6 wherein Z is NR.

8. The method of claim 7 wherein  $Ar^2$  is a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is



wherein  $R^b$  is a noninterfering substituent and  $n$  is an integer of 0-5; and/or

5 L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or  
the dotted line represents a  $\pi$  bond.

9. The method of claim 7 wherein each  $R^b$  is independently halo, OR, SR,  
10 NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system.

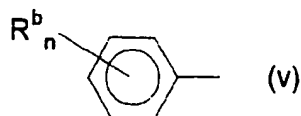
10. The method of claim 7 wherein  
m is 0; and/or  
15 each  $R^b$  is independently OR, SR or halo;  
where  $n=2$  and at least one  $R^b$  is OR or SR; and/or  
L is -NHCO- or -CR=CR-.

11. The method of claim 7 wherein said compound is 59-0100, 59-103,  
20 59-104, 59-105 or 59-106.

12. The method of claim 6 wherein Z is S.

13. The method of claim 12 wherein  $Ar^2$  is a substituted or unsubstituted  
25 aromatic system containing a 6-membered heterocycle or is of the formula





wherein  $R^b$  is a noninterfering substituent and  $n$  is an integer of 0-5; and/or

$L$  is  $-N=N-$ ,  $-N=CR-$ ,  $-RC=CR-$ ,  $-NRNR-$ ,  $-CR_2NR-$ ,  $-CR_2CR_2-$ ,  $-NRCO-$  or  $-CONR-$  where  $R$  is H or alkyl (1-6C); and/or

5 the dotted line represents a  $\pi$  bond.

14. The method of claim 13 wherein each  $R^b$  is independently halo, OR, SR,  $NR_2$ ,  $NO$ ,  $NO_2$ ,  $OCF_3$  or  $CF_3$  wherein  $R$  is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system.

10

15. The method of claim 13 wherein

$m$  is 0; and/or

each  $R^b$  is independently OR, SR or halo;

where  $n=2$  and at least one  $R^b$  is OR or SR; and/or

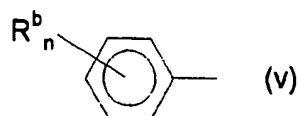
15  $L$  is  $-NHCO-$  or  $-CR=CR-$ .

16. The method of claim 12 wherein the compound is compound number 59-002, 59-0070, 59-0072, 59-0099, the benzothiazole counterpart of 59-0104, 59-0102, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195, 20 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210.

17. The method of claim 16 wherein the compound is the benzothiazole counterpart of 59-0104, or is compound number 59-0147, 59-0205 or 59-0210.

25 18. The method of claim 6 wherein  $Z$  is CR or  $CR_2$ .

19. The method of claim 18 wherein  $Ar^2$  is



wherein  $R^b$  is a noninterfering substituent and  $n$  is an integer of 0-5; and/or

$L$  is  $-N=N-$ ,  $-N=CR-$ ,  $-RC=CR-$ ,  $-NRNR-$ ,  $-CR_2NR-$ ,  $-CR_2CR_2-$ ,  $-NRCO-$  or  $-CONR-$  where  $R$  is H or alkyl (1-6C); and/or

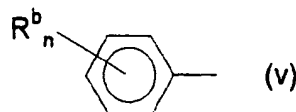
5 the dotted line represents a  $\pi$  bond.

20. The method of claim 19 wherein each  $R^b$  is independently halo, OR, SR,  $NR_2$ , NO,  $NO_2$ ,  $OCF_3$  or  $CF_3$  wherein  $R$  is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system.

10

21. The method of claim 6 wherein  $Z$  is O.

22. The method of claim 21 wherein  $Ar^2$  is of the formula



15 wherein  $R^b$  is a noninterfering substituent and  $n$  is an integer of 0-5; and/or

$L$  is  $-N=N-$ ,  $-N=CR-$ ,  $-RC=CR-$ ,  $-NRNR-$ ,  $-CR_2NR-$ ,  $-CR_2CR_2-$ ,  $-NRCO-$  or  $-CONR-$  where  $R$  is H or alkyl (1-6C); and/or

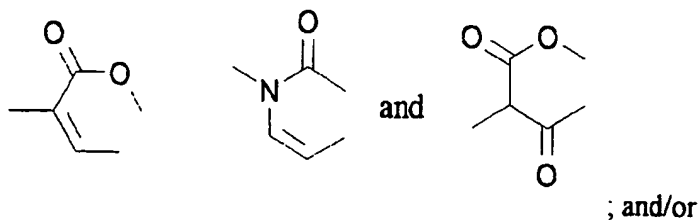
the dotted line represents a  $\pi$  bond.

20 23. The method of claim 19 wherein each  $R^b$  is independently halo, OR, SR,  $NR_2$ , NO,  $NO_2$ ,  $OCF_3$  or  $CF_3$  wherein  $R$  is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system.

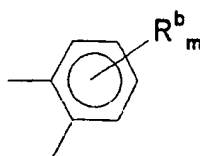
24. The method of claim 21 wherein the compound of formula (1) is  
25 compound number 896-5005.

25. The method of claim 5 wherein L is a constrained linker.

26. The method of claim 25 wherein Z is S or NR; and/or  
 5 wherein L is selected from the group consisting of



wherein Ar<sup>2</sup> is

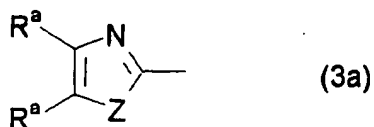


wherein R<sup>b</sup> is a noninterfering substituent and m is 0-4.

27. The method of claim 25 wherein each R<sup>b</sup> is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or comprises an aromatic system.

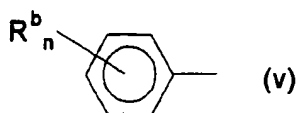
28. The method of claim 25 wherein the compound of formula (1) is 59-0124.

29. The method of any of claims 1-4 wherein Ar<sup>1</sup> is of the formula



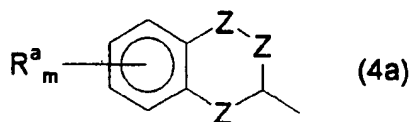
wherein each R<sup>a</sup> is independently a noninterfering substituent or is H; and  
 Z is NR, S or O, wherein R is alkyl (1-6C) or H.

30. The method of claim 29 wherein Z is S; and/or  
wherein Ar<sup>2</sup> is



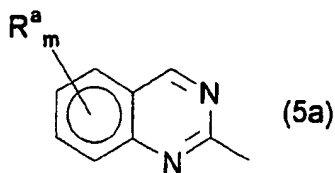
- 5 wherein R<sup>b</sup> is a noninterfering substituent and n is an integer of 0-5; and/or  
L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NRCO- or  
-CONR- where R is H or alkyl (1-6C); and/or  
the dotted line represents a  $\pi$  bond; and/or  
each R<sup>b</sup> is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein  
10 R is H or alkyl (1-6C) or comprises an aromatic system.

31. The method of any of claims 1-4 wherein Ar<sup>1</sup> is

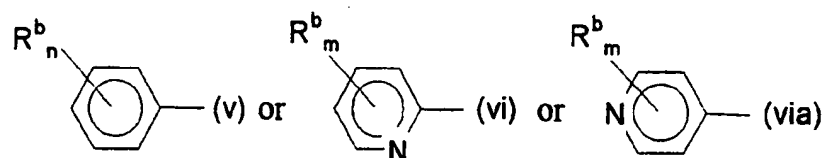


- wherein R<sup>a</sup> is a noninterfering substituent;  
15 m is an integer of 0-4;  
each dotted line represents an optional  $\pi$ -bond;  
each Z is independently N, NR, CR or CR<sub>2</sub>, where each R is independently H  
or alkyl (1-6C) with the proviso that at least one Z is N or NR.

20 32. The method of claim 31 wherein Ar<sup>1</sup> is



33. The method of claim 31 wherein  $Ar_2$  is



wherein each  $R^b$  is independently a noninterfering substituent, and  $n$  is 0-5 and  $m$  is 0-4; and/or

5 L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NR<sub>2</sub>CR<sub>2</sub>-, -NR<sub>2</sub>CR<sub>2</sub>CR<sub>2</sub>-,  
 -NR<sub>2</sub>CR<sub>2</sub>CO-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NR<sub>2</sub>CR<sub>2</sub>CR<sub>2</sub>NR-, -NR<sub>2</sub>CR=CRNR- or  
 -NR<sub>2</sub>COCR<sub>2</sub>NR-.

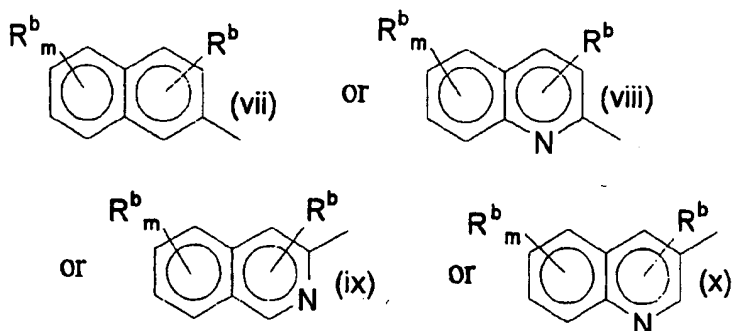
34. The method of claim 33 wherein each  $R^b$  is independently halo, OR,  
 10 SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $R^b$  comprises an  
 aromatic system.

35. The method of claim 32 wherein  
 each  $R^b$  is NR<sub>2</sub> or OR and  $m$  and  $n$  are 0, 1 or 2; and/or  
 15 L is -CR=CR-, -N=N- or -NR<sub>2</sub>CO-.

36. The method of claim 35 wherein the compound of formula (1) is  
 59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 59-0197, 59-0198, 59-0199 or  
 59-0480.

20

37. The method of claim 31 wherein  $Ar_2$  is substituted or unsubstituted  
 quinolyl or naphthyl of the formula



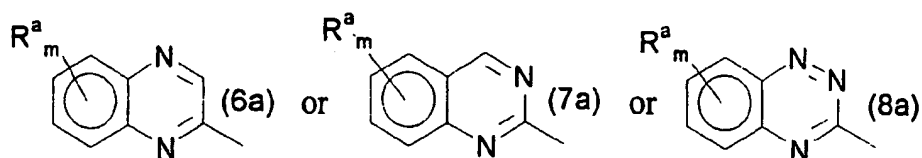
wherein each  $R^b$  is a noninterfering substituent and  $m$  is 0-4.

38. The method of claim 37 wherein  $L$  is  $-N=N-$ ,  $-RC=CR-$ ,  $-RC=N-$ ,  
 5  $-NRCO-$ ,  $-NRCR_2-$ ,  $-NRCR_2CR_2-$ ,  $-NRCR_2CO-$ ,  $-NRNR-$ ,  $-CR_2CR_2-$ ,  
 $-NRCR_2CR_2NR-$ ,  $-NRCR=CRNR-$  or  $-NRCOCR_2NR-$ ; and/or

wherein each  $R^b$  is independently halo, OR, SR,  $NR_2$ , NO,  $NO_2$ ,  $OCF_3$  or  $CF_3$   
 wherein  $R$  is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system and  $m$  is 0, 1 or 2.

- 10 39. The method of claim 38 wherein the compound of formula (1) is  
 59-0089, 59-0090, 59-0092 or 59-0094.

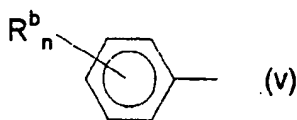
40. The method of claim 31 wherein  $Ar^1$  is



- 15 wherein each  $R^a$  is a noninterfering substituent and  $m$  is 0-4.

41. The method of claim 40 wherein  $L$  is  $-N=N-$ ,  $-RC=CR-$ ,  $-RC=N-$ ,  
 $-NRCO-$ ,  $-NRCR_2-$ ,  $-NRCR_2CR_2-$ ,  $-NRCR_2CO-$ ,  $-NRNR-$ ,  $-CR_2CR_2-$ ,  
 $-NRCR_2CR_2NR-$ ,  $-NRCR=CRNR-$  or  $-NRCOCR_2NR-$ ; and/or

- 20  $Ar^2$  is



wherein  $R^b$  is a noninterfering substituent and  $n$  is an integer of 0-5; and/or  
 wherein each  $R^b$  is independently halo, OR, SR,  $NR_2$ , NO,  $NO_2$ ,  $OCF_3$  or  $CF_3$   
 wherein  $R$  is H or alkyl (1-6C) or  $R^b$  comprises an aromatic system.

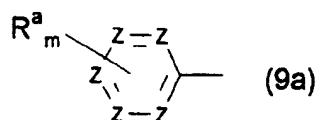
5

42. The method of claim 41 wherein the compound of formula (1) is  
 59-203, 59-285 or 59-286.

43. The method of claim 31 wherein  $L$  is a constrained linker.

10

44. The method of any of claims 1-4 wherein  $Ar^1$  is



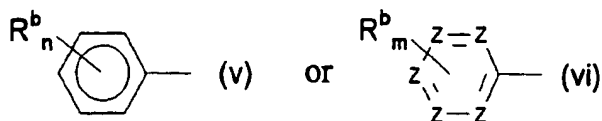
wherein each  $R^a$  is independently a noninterfering substituent;  
 $m$  is an integer of 0-4;  
 each  $Z$  is independently N or CR, where  $R$  is H or alkyl (1-6C), with the  
 proviso that at least one  $Z$  must be N and at least one  $Z$  must be CR.

15

45. The method of claim 44 wherein  $L$  is a flexible conjugating or  
 nonconjugating linker; and/or

20

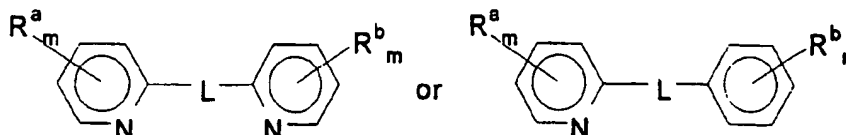
wherein  $Ar^2$  is



wherein each  $R^b$  is independently a noninterfering substituent, and

in (vi) each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

46. The method of claim 45 wherein the compound of formula (1) is of the  
5 formula



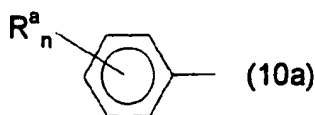
47. The method of claim 46 wherein L is -N=N-, -RC=CR-, -RC=N-,  
-NRCO-, -NRCR<sub>2</sub>-, -NRCR<sub>2</sub>CR<sub>2</sub>-, -NRCR<sub>2</sub>CO-, -NRNR-, -CR<sub>2</sub>CR<sub>2</sub>-,  
10 -NRCR<sub>2</sub>CR<sub>2</sub>NR-, -NRCR=CRNR- or -NRCOCR<sub>2</sub>NR-, and/or  
wherein each R<sup>a</sup> and R<sup>b</sup> is independently halo, OR, SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub>  
or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or R<sup>b</sup> comprises an aromatic system and each m  
and n is independently 0, 1 or 2.

48. The method of claim 47 wherein L is -NHCR<sub>2</sub>CR<sub>2</sub>NH-, m is 1 and R<sup>a</sup> is  
15 CF<sub>3</sub> para to L.

49. The method of claim 48 wherein the compound of formula (1) is  
59-0145, 59-0450, 59-0459 or 59-0483.

20

50. The method of any of claims 1-4 wherein Ar<sup>1</sup> is



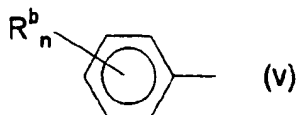
wherein each R<sup>a</sup> is a noninterfering substituent; and

n is an integer of 0 and 5, and

- 25 wherein L is a flexible linker that contains at least one nitrogen; and/or



wherein  $\text{Ar}^2$  is of the formula



and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NR<sub>2</sub>CR<sub>2</sub>-, -NR<sub>2</sub>CR<sub>2</sub>CR<sub>2</sub>-,  
 -NR<sub>2</sub>CR<sub>2</sub>CO-, -NR<sub>2</sub>NR<sub>2</sub>CR<sub>2</sub>CR<sub>2</sub>-, -NR<sub>2</sub>NR<sub>2</sub>CR=CR-, -NR<sub>2</sub>NR<sub>2</sub>COCR<sub>2</sub>-,  
 5 -NR<sub>2</sub>NR<sub>2</sub>COCR=CR-, -NR<sub>2</sub>NR<sub>2</sub>CSCR<sub>2</sub>-, -NR<sub>2</sub>NR<sub>2</sub>CSCR=CR-, -NR<sub>2</sub>NR<sub>2</sub>CONR-,  
 -NR<sub>2</sub>NR<sub>2</sub>CSNR-, -NR<sub>2</sub>NR-, -CR<sub>2</sub>CR<sub>2</sub>-, -NR<sub>2</sub>CR<sub>2</sub>CR<sub>2</sub>NR-, -NR<sub>2</sub>CR=CRNR- or  
 -NR<sub>2</sub>COCR<sub>2</sub>NR-.

51. The method of claim 50 wherein each  $\text{R}^b$  is independently halo, OR,  
 10 SR, NR<sub>2</sub>, NO, NO<sub>2</sub>, OCF<sub>3</sub> or CF<sub>3</sub> wherein R is H or alkyl (1-6C) or  $\text{R}^b$  comprises an  
 aromatic system.

52. The method of claim 50 wherein L is -CR=CRCONRNR-,  
 -CR=CRCSNRNR-, -CR<sub>2</sub>CONRNR- -CR<sub>2</sub>CSNRNR-, -NRNRCONR- or  
 15 -NRNRCSNR- and/or

$\text{R}^b$  is -NR<sub>2</sub> and n=1 wherein  $\text{R}^b$  is in the para position.

53. The method of claim 50 wherein  $\text{R}^a$  is -COOR and m is 1.

20 54. The method of claim 52 wherein the compound of formula (1) is  
 59-0045, 59-0095, 59-0096, 59-0097 or 59-0098.

55. A pharmaceutical composition for use in a method to treat a condition  
 in a vertebrate animal characterized by a deficiency in, or need for, bone growth  
 25 replacement and/or an undesirable level of bone resorption which composition contains  
 a pharmaceutically acceptable excipient and an effective amount of a compound of the  
 formula set forth in any preceding claim.

56. A compound for use in preparing a composition for use in the treatment of a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption which method comprises administering said composition to a vertebrate subject, said compound set
- 5 forth in any preceding claim.

1/146

Ar <sup>1</sup> - linker - Ar <sup>2</sup> 1.5 - 15Å		(I)
Ar <sup>1</sup>	Ar <sup>2</sup>	
contains 5-membered heterocycle	substituted or unsubstituted benzene	II-A
contains 5-membered heterocycle	substituted or unsubstituted naphthalene	II-B
contains 5-membered heterocycle	contains 6-membered heterocycle	II-C
contains 5-membered heterocycle	contains 5-membered heterocycle	II-D
contains 6-membered heterocycle	substituted or unsubstituted benzene	II-E
contains 6-membered heterocycle	substituted or unsubstituted naphthalene	II-F
contains 6-membered heterocycle	contains 6-membered heterocycle	II-G
substituted or unsubstituted naphthalene	substituted or unsubstituted benzene	II-H
substituted or unsubstituted naphthalene	substituted or unsubstituted naphthalene	II-I
substituted or unsubstituted benzene	substituted or unsubstituted benzene	II-J

Figure 1

2/146

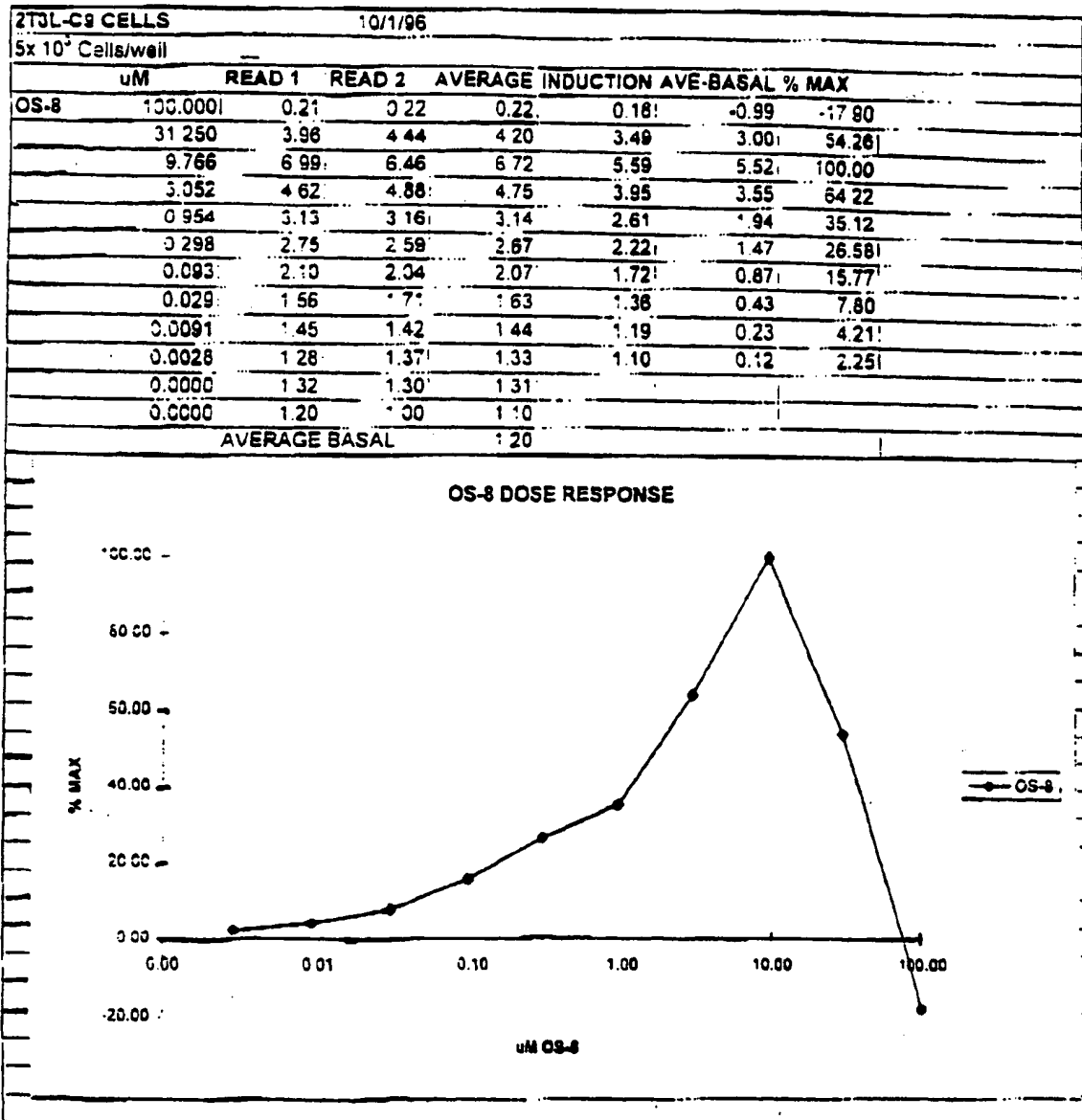


Figure 2

3/146

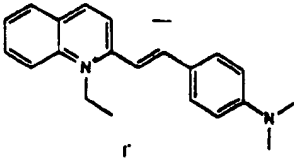
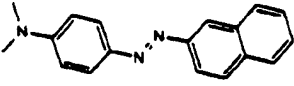
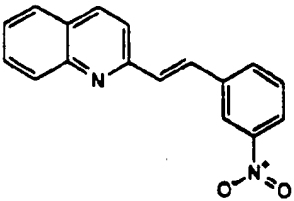
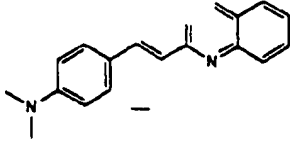
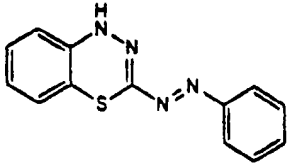
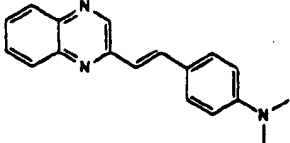
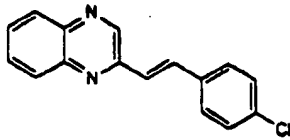
NINC	MOL.WEIGHT	Concentration	% Response
	430.33		
		100.00 $\mu$ M	-19.190
		31.25 $\mu$ M	32.450
		9.77 $\mu$ M	-14.240
		3.05 $\mu$ M	-11.330
		953.67 nM	-12.790
		298.02 nM	-13.450
		93.13 nM	-12.290
		29.10 nM	-9.440
		9.09 nM	-6.450
		2.84 nM	-5.130
		888.18 pM	-3.320
	275.36		
		100.00 $\mu$ M	-4.630
		31.25 $\mu$ M	16.790
		9.77 $\mu$ M	62.830
		3.05 $\mu$ M	102.720
		953.67 nM	60.860
		298.02 nM	32.460
		93.13 nM	19.340
		29.10 nM	17.220
		9.09 nM	5.640
		2.84 nM	4.840
		888.18 pM	5.640
	276.30		
		100.00 $\mu$ M	-16.210
		31.25 $\mu$ M	-8.580
		9.77 $\mu$ M	11.620
		3.05 $\mu$ M	27.790
		953.67 nM	18.390
		298.02 nM	6.230
		93.13 nM	12.420
		29.10 nM	12.630
		9.09 nM	6.990
		2.84 nM	7.970
		888.18 pM	5.060

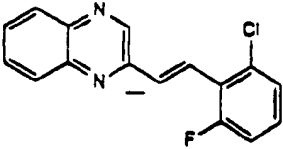
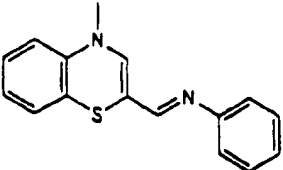
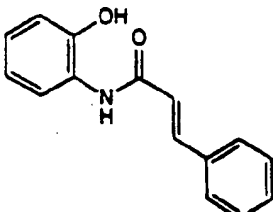
Figure 3

4/146

					
50-0197	274.37				
50-0197		100.00 $\mu$ M	-18.250		
		31.25 $\mu$ M	-14.980		
		9.77 $\mu$ M	4.040		
		3.05 $\mu$ M	93.790		
		953.67 nM	205.630		
		298.02 nM	242.920		
		93.13 nM	195.890		
		29.10 nM	115.320		
		9.09 nM	85.630		
		2.84 nM	54.380		
		888.18 pM	33.180		
					
59-0008	254.32				
					
59-0019	59-0019				
59-0019		100.00 $\mu$ M	-22.240		
		31.25 $\mu$ M	-22.670		
		9.77 $\mu$ M	-17.470		
		3.05 $\mu$ M	74.480		
		953.67 nM	198.080		
		298.02 nM	258.340		
		93.13 nM	225.350		
		29.10 nM	75.220		
		9.09 nM	24.030		
		2.84 nM	34.480		
		888.18 pM	-3.740		
					
59-0020	266.73				
59-0020		100.00 $\mu$ M	-18.510		
		31.25 $\mu$ M	-16.040		
		9.77 $\mu$ M	-0.270		
		3.05 $\mu$ M	99.490		
		953.67 nM	153.320		
		298.02 nM	110.240		
		93.13 nM	60.030		

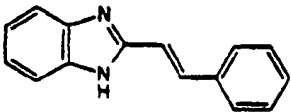
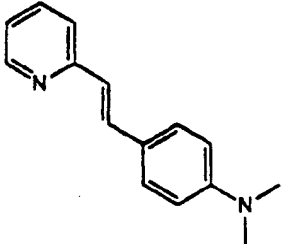
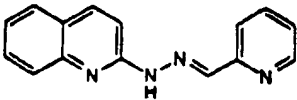
5/146

		29.10 nM	37.870
		9.09 nM	24.820
		2.84 nM	20.500
		888.18 pM	13.310

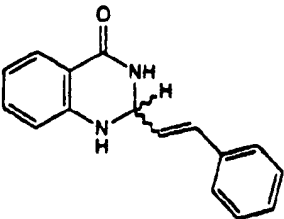
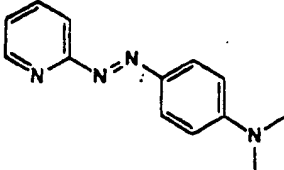
					
59-0021	284.72				
59-0021		100.00 $\mu$ M	-18.310		
		31.25 $\mu$ M	-12.850		
		9.77 $\mu$ M	84.130		
		3.05 $\mu$ M	89.940		
		953.67 nM	65.760		
		298.02 nM	33.940		
		93.13 nM	22.960		
		29.10 nM	25.020		
		9.09 nM	13.910		
		2.84 nM	33.270		
		888.18 pM	15.500		
					
59-0022	268.37				
59-0022		100.00 $\mu$ M	7.250		
		31.25 $\mu$ M	-2.070		
		9.77 $\mu$ M	-0.270		
		3.05 $\mu$ M	4.390		
		953.67 nM	3.060		
		298.02 nM	-1.800		
		93.13 nM	-0.200		
		29.10 nM	-3.270		
		9.09 nM	1.130		
		2.84 nM	2.590		
		888.18 pM	2.460		
					
59-0023	239.28				
59-0023		100.00 $\mu$ M	-12.720		
		31.25 $\mu$ M	33.140		
		9.77 $\mu$ M	56.500		
		3.05 $\mu$ M	29.850		
		953.67 nM	25.360		
		298.02 nM	15.700		
		93.13 nM	7.380		
		29.10 nM	-9.710		
		9.09 nM	1.000		
		2.84 nM	4.520		
		888.18 pM	-0.010		



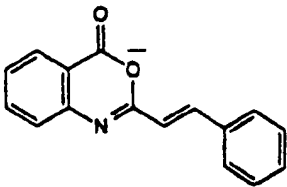
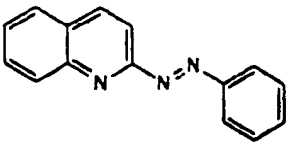
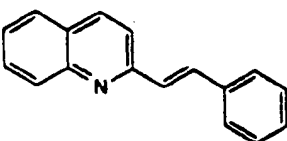
71146

					
59-0024	220.28				
					
59-0025	224.31				
59-0025		100.00 $\mu$ M	-25.590		
		31.25 $\mu$ M	14.150		
		9.77 $\mu$ M	50.690		
		3.05 $\mu$ M	57.880		
		953.67 nM	38.900		
		298.02 nM	28.530		
		93.13 nM	19.680		
		29.10 nM	17.490		
		9.09 nM	-0.600		
		2.84 nM	-4.190		
		888.18 pM	4.670		
					
59-0026	248.29				
59-0026		100.00 $\mu$ M	-29.830		
		31.25 $\mu$ M	-9.440		
		9.77 $\mu$ M	-10.470		
		3.05 $\mu$ M	46.220		
		953.67 nM	107.760		
		298.02 nM	86.720		
		93.13 nM	36.850		
		29.10 nM	26.720		
		9.09 nM	8.520		
		2.84 nM	-1.240		
		888.18 pM	4.020		

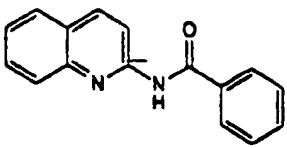
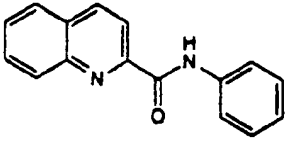
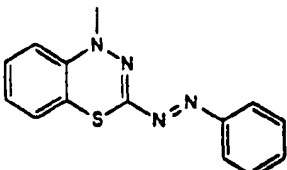
8/146

					
59-0027	250.30				
59-0027		100.00 $\mu$ M	89.810		
		31.25 $\mu$ M	54.670		
		9.77 $\mu$ M	44.940		
		3.05 $\mu$ M	23.780		
		953.67 nM	8.380		
		298.02 nM	6.330		
		93.13 nM	7.380		
		29.10 nM	3.380		
		9.09 nM	-1.620		
		2.84 nM	-3.670		
		888.18 pM	-0.720		
					
59-0028	226.28				
59-0028		100.00 $\mu$ M	-26.750		
		31.25 $\mu$ M	-16.740		
		9.77 $\mu$ M	29.550		
		3.05 $\mu$ M	100.580		
		953.67 nM	54.940		
		298.02 nM	31.340		
		93.13 nM	7.500		
		29.10 nM	7.500		
		9.09 nM	7.880		
		2.84 nM	3.140		
		888.18 pM	4.670		

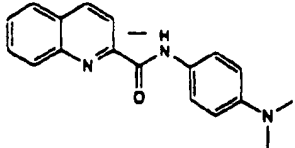
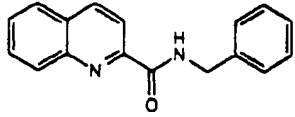
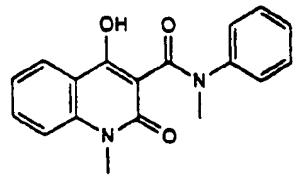
9/146

					
59-0029	249.27				
59-0029		100.00 $\mu$ M	-15.160		
		31.25 $\mu$ M	41.940		
		9.77 $\mu$ M	36.830		
		3.05 $\mu$ M	7.120		
		953.67 nM	21.880		
		298.02 nM	15.840		
		93.13 nM	1.810		
		29.10 nM	1.370		
		9.09 nM	12.140		
		2.84 nM	-4.230		
		888.18 pM	9.040		
					
59-0030 A	233.28				
59-0030 A		100.00 $\mu$ M	-27.970		
		31.25 $\mu$ M	-22.830		
		9.77 $\mu$ M	-5.420		
		3.05 $\mu$ M	57.280		
		953.67 nM	72.620		
		298.02 nM	53.000		
		93.13 nM	29.990		
		29.10 nM	14.630		
		9.09 nM	3.870		
		2.84 nM	6.970		
		888.18 pM	1.810		
					
59-0031	231.30				
59-0031		100.00 $\mu$ M	-25.790		
		31.25 $\mu$ M	-17.810		
		9.77 $\mu$ M	20.840		
		3.05 $\mu$ M	87.380		
		953.67 nM	49.320		
		298.02 nM	43.110		
		93.13 nM	29.530		
		29.10 nM	1.810		
		9.09 nM	1.220		
		2.84 nM	-0.550		
		888.18 pM	4.160		

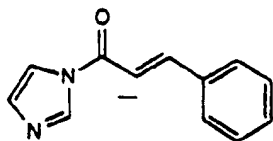
10 / 146

					
59-0032	248.29				
59-0032		100.00 $\mu$ M	-7.780		
		31.25 $\mu$ M	40.750		
		9.77 $\mu$ M	42.820		
		3.05 $\mu$ M	25.700		
		953.67 nM	31.170		
		298.02 nM	34.410		
		93.13 nM	3.570		
		29.10 nM	4.320		
		9.09 nM	-10.000		
		2.84 nM	5.650		
		888.18 pM	11.990		
					
59-0033	248.29				
59-0033		100.00 $\mu$ M	-28.180		
		31.25 $\mu$ M	-11.990		
		9.77 $\mu$ M	55.300		
		3.05 $\mu$ M	49.710		
		953.67 nM	47.410		
		298.02 nM	0.250		
		93.13 nM	7.980		
		29.10 nM	-8.940		
		9.09 nM	-7.630		
		2.84 nM	-0.400		
		888.18 pM	-5.980		
					
59-0034	288.34				
59-0034		100.00 $\mu$ M	-28.51		
		31.25 $\mu$ M	24		
		9.77 $\mu$ M	73.58		
		3.05 $\mu$ M	37.91		
		953.67 nM	20.09		
		298.02 nM	16.87		
		93.13 nM	15.23		
		29.10 nM	28.83		
		9.09 nM	9.08		
		2.84 nM	23.02		
		888.18 pM	-0.32		

11 / 146

			
59-0035	291.36		
59-0035		100.00 $\mu$ M	-14.92
		31.25 $\mu$ M	29.17
		9.77 $\mu$ M	15.87
		3.05 $\mu$ M	18.81
		953.67 nM	3.88
		298.02 nM	6.16
		93.13 nM	3.22
		29.10 nM	-10.03
		9.09 nM	15.58
		2.84 nM	-3.58
		888.18 pM	-7.13
			
59-0036	282.31		
59-0036		100.00 $\mu$ M	-0.98
		31.25 $\mu$ M	-3.25
		9.77 $\mu$ M	-4.54
		3.05 $\mu$ M	-1.95
		953.67 nM	0.32
		298.02 nM	-6.49
		93.13 nM	-17.19
		29.10 nM	-0.66
		9.09 nM	-5.52
		2.84 nM	-9.41
		888.18 pM	-16.53
			
59-0037	308.00		
59-0037		100.00 $\mu$ M	-10.69
		31.25 $\mu$ M	-11.99
		9.77 $\mu$ M	-10.03
		3.05 $\mu$ M	-19.11
		953.67 nM	-9.41
		298.02 nM	2.27
		93.13 nM	-2.91
		29.10 nM	-10.69
		9.09 nM	2.59
		2.84 nM	-0.86
		888.18 pM	-2.59

12 / 146

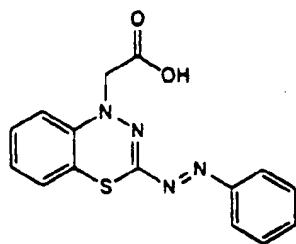


59-0038

291.36

59-0038

	100.00 $\mu$ M	-23.430
	31.25 $\mu$ M	-8.390
	9.77 $\mu$ M	-0.100
	3.05 $\mu$ M	-2.880
	953.67 nM	-2.240
	298.02 nM	3.900
	93.13 nM	6.350
	29.10 nM	1.150
	9.09 nM	6.960
	2.84 nM	-4.390
	888.18 pM	-0.380

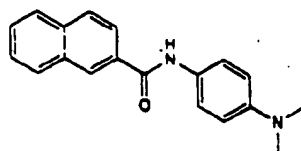


59-0039

312.35

59-0039

	100.00 $\mu$ M	14.170
	31.25 $\mu$ M	7.620
	9.77 $\mu$ M	1.940
	3.05 $\mu$ M	-3.140
	953.67 nM	-7.770
	298.02 nM	-5.980
	93.13 nM	-8.820
	29.10 nM	-2.390
	9.09 nM	-16.580
	2.84 nM	-4.480
	888.18 pM	-0.450



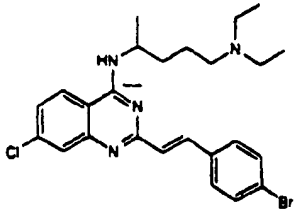
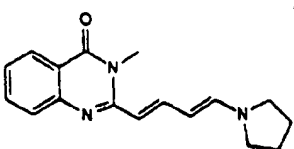
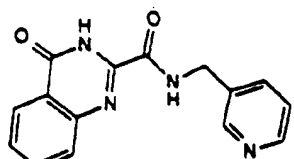
59-0040

290.37

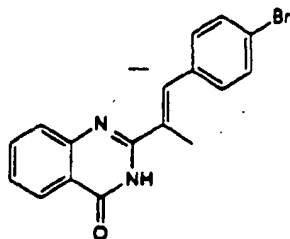
59-0040

	100.00 $\mu$ M	-20.400
	31.25 $\mu$ M	-17.310
	9.77 $\mu$ M	-8.110
	3.05 $\mu$ M	32.180
	953.67 nM	38.180
	298.02 nM	17.440
	93.13 nM	2.040
	29.10 nM	10.350
	9.09 nM	-8.070
	2.84 nM	6.960
	888.18 pM	13.440

13/146

				
59-0041	501.90			
59-0041		100.00 $\mu$ M	-18.37	
		31.25 $\mu$ M	-17.33	
		9.77 $\mu$ M	-5.11	
		3.05 $\mu$ M	3.31	
		953.67 nM	-0.77	
		298.02 nM	-1.56	
		93.13 nM	3.55	
		29.10 nM	-11.24	
		9.09 nM	0.25	
		2.84 nM	-0.27	
		888.18 pM	2.02	
				
59-0042	281.36			
59-0042		100.00 $\mu$ M	163.51	
		31.25 $\mu$ M	-7.67	
		9.77 $\mu$ M	9.41	
		3.05 $\mu$ M	0.75	
		953.67 nM	6.11	
		298.02 nM	3.82	
		93.13 nM	2.54	
		29.10 nM	4.07	
		9.09 nM	-9.73	
		2.84 nM	-0.02	
		888.18 pM	18.37	
				
59-0043	280.29			
59-0043		100.00 $\mu$ M	20.66	
		31.25 $\mu$ M	7.4	
		9.77 $\mu$ M	-1.29	
		3.05 $\mu$ M	-2.31	
		953.67 nM	1.64	
		298.02 nM	-0.79	
		93.13 nM	1.52	
		29.10 nM	2.79	
		9.09 nM	-0.27	
		2.84 nM	6.92	
		888.18 pM	-4.34	

14/146

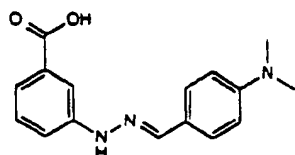


59-0044

341.21

59-0044

100.00 $\mu$ M	7.38
31.25 $\mu$ M	11.72
9.77 $\mu$ M	12.49
3.05 $\mu$ M	-0.52
953.67 nM	0.5
298.02 nM	6.11
93.13 nM	-1.54
29.10 nM	19.14
9.09 nM	7.13
2.84 nM	-2.06
888.16 pM	5.84

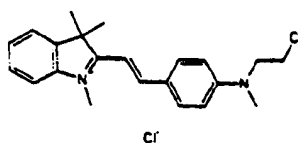


59-0045

283.33

59-0045

100.00 $\mu$ M	52.37	64.460
31.25 $\mu$ M	148.43	192.960
9.77 $\mu$ M	204.47	422.540
3.05 $\mu$ M	280.3	437.020
953.67 nM	254.82	410.890
298.02 nM	218.21	268.090
93.13 nM	196.98	183.730
29.10 nM	96.06	80.440
9.09 nM	67.35	55.530
2.84 nM	52.99	44.160



59-0046

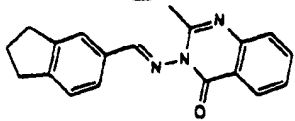
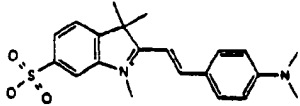
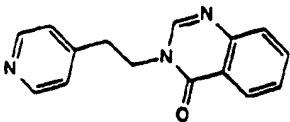
389.37

59-0046

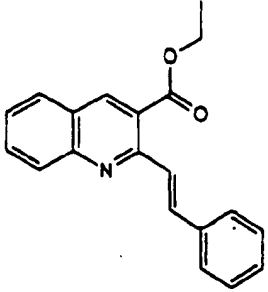
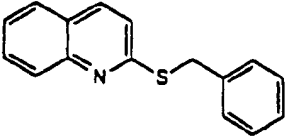
100.00 $\mu$ M	79.33
31.25 $\mu$ M	2.24
9.77 $\mu$ M	-1.67
3.05 $\mu$ M	-6.18
953.67 nM	0.001
298.02 nM	-3.63
93.13 nM	-0.84
29.10 nM	-8.42
9.09 nM	-3.92
2.84 nM	0.3
888.16 pM	5.61



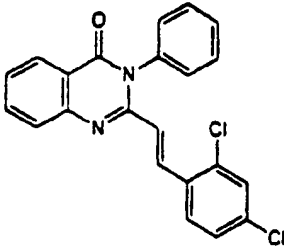
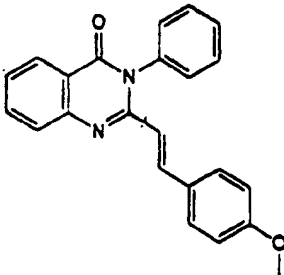
15 / 146

					
59-0047	303.37				
59-0047		100.00 $\mu$ M	-6.73		
		31.25 $\mu$ M	10.38		
		9.77 $\mu$ M	-6.16		
		3.05 $\mu$ M	-1.39		
		953.67 nM	-10.11		
		298.02 nM	-4.49		
		93.13 nM	-7.28		
		29.10 nM	-12.34		
		9.09 nM	-3.08		
		2.84 nM	-2.26		
		888.18 pM	-5.34		
					
59-0048	384.50				
59-0048		100.00 $\mu$ M	-6.73		
		31.25 $\mu$ M	0.27		
		9.77 $\mu$ M	-5.61		
		3.05 $\mu$ M	-2.26		
		953.67 nM	-12.89		
		298.02 nM	-1.69		
		93.13 nM	-4.77		
		29.10 nM	-8.14		
		9.09 nM	-3.92		
		2.84 nM	-11.2		
		888.18 pM	-4.77		
					
59-0049	251.29				
59-0049		100.00 $\mu$ M	4.49		
		31.25 $\mu$ M	0		
		9.77 $\mu$ M	-4.77		
		3.05 $\mu$ M	1.96		
		953.67 nM	8.69		
		298.02 nM	-5.04		
		93.13 nM	-2.24		
		29.10 nM	1.69		
		9.09 nM	-4.49		
		2.84 nM	2.24		
		888.18 pM	-0.31		

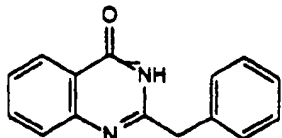
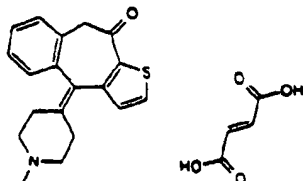
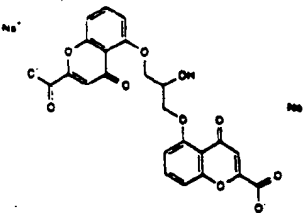
16 / 146

					
59-0050	303.36				
59-0050		100.00µM		45.79	
		31.25µM		10.02	
		9.77µM		11.29	
		3.05µM		-4.68	
		953.67nM		-6.92	
		298.02nM		-5.65	
		93.13nM		1.69	
		29.10nM		-7.57	
		9.09nM		-12.05	
		2.84nM		-13.63	
		888.18pM		5.2	
					
59-0051	251.35				
59-0051		100.00µM		32.35	
		31.25µM		-18.42	
		9.77µM		-0.55	
		3.05µM		-13.94	
		953.67nM		-12.02	
		298.02nM		-14.59	
		93.13nM		-7.55	
		29.10nM		-11.4	
		9.09nM		-14.91	
		2.84nM		-10.74	
		888.18pM		-20.03	

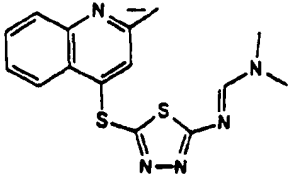
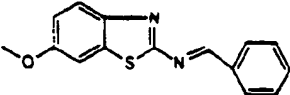
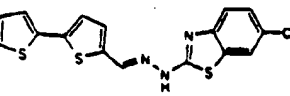
17/146

					
59-0052	393.28				
59-0052		100.00 uM		-21.62	
		31.25 uM		-13.32	
		9.77 uM		-21.31	
		3.05 uM		-11.08	
		953.67 nM		-20.66	
		298.02 nM		-17.14	
		93.13 nM		-16.49	
		29.10 nM		-11.4	
		9.09 nM		-10.74	
		2.84 nM		-11.08	
		888.18 pM		-14.59	
					
59-0053	354.41				
59-0053		100.00 uM		-17.14	
		31.25 uM		-21.31	
		9.77 uM		-9.47	
		3.05 uM		-11.08	
		953.67 nM		-0.83	
		298.02 nM		-11.4	
		93.13 nM		-9.47	
		29.10 nM		-19.72	
		9.09 nM		-18.45	
		2.84 nM		-10.09	
		888.18 pM		-2.76	

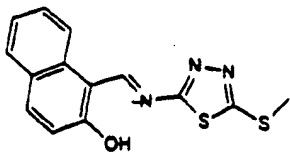
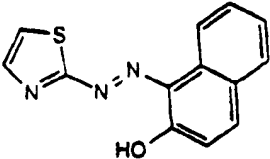
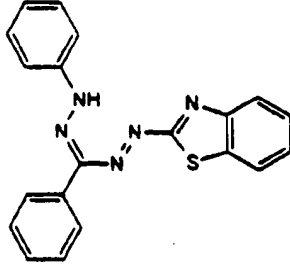
18/146

					
59-0054	236.28				
59-0054		100.00 $\mu$ M	-20.04		
		31.25 $\mu$ M	-6.95		
		9.77 $\mu$ M	8.31		
		3.05 $\mu$ M	-3.37		
		953.67 nM	-2.41		
		298.02 nM	-0.99		
		93.13 nM	-0.99		
		29.10 nM	-1.94		
		9.09 nM	5.92		
		2.84 nM	-2.17		
		888.18 pM	-9.31		
					
59-0055	425.51				
59-0055		100.00 $\mu$ M	-13.76		
		31.25 $\mu$ M	-9.51		
		9.77 $\mu$ M	-2.02		
		3.05 $\mu$ M	3.24		
		953.67 nM	-6.27		
		298.02 nM	-4.05		
		93.13 nM	-1.62		
		29.10 nM	-7.49		
		9.09 nM	-7.09		
		2.84 nM	-3.04		
					
59-0056	512.34				
59-0056		100.00 $\mu$ M	-1.42		
		31.25 $\mu$ M	-4.87		
		9.77 $\mu$ M	0.18		
		3.05 $\mu$ M	3.84		
		953.67 nM	-6.07		
		298.02 nM	-7.29		
		93.13 nM	0.001		
		29.10 nM	-4.25		
		9.09 nM	-1.02		
		2.84 nM	-3.85		

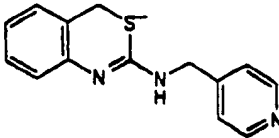
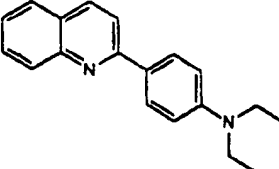
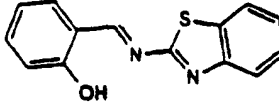
19/146

			
59-0057			
59-0057	100.00 $\mu$ M	-24.1501	
	31.25 $\mu$ M	-24.3001	
	9.77 $\mu$ M	-5.6801	
	3.05 $\mu$ M	-11.5001	
	953.67 nM	-13.0001	
	298.02 nM	-6.2801	
	93.13 nM	-12.5501	
	29.10 nM	-6.8701	
	9.09 nM	-8.5201	
	2.84 nM	-16.2901	
			
59-0058			
59-0058	100.00 $\mu$ M	4.1701	
	31.25 $\mu$ M	7.6201	
	9.77 $\mu$ M	-1.7901	
	3.05 $\mu$ M	-7.3201	
	953.67 nM	-1.9401	
	298.02 nM	-6.8701	
	93.13 nM	-1.4901	
	29.10 nM	-8.3701	
	9.09 nM	-5.0801	
	2.84 nM	-12.4001	
			
59-0059			
59-0059	100.00 $\mu$ M	-18.7701	
	31.25 $\mu$ M	-16.1401	
	9.77 $\mu$ M	-3.0901	
	3.05 $\mu$ M	0.1501	
	953.67 nM	6.0101	
	298.02 nM	-1.9101	
	93.13 nM	-1.7801	
	29.10 nM	-9.1001	
	9.09 nM	-8.2201	
	2.84 nM	-5.7201	

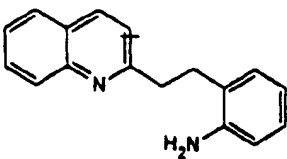
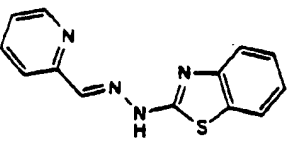
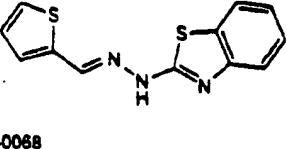
20/146

			
59-0060			
59-0060	100.00 $\mu$ M	-4.250	
	31.25 $\mu$ M	-14.520	
	9.77 $\mu$ M	1.030	
	3.05 $\mu$ M	-1.180	
	953.67 nM	-13.200	
	298.02 nM	-0.740	
	93.13 nM	-3.870	
	29.10 nM	-7.340	
	9.09 nM	-1.310	
	2.84 nM	0.290	
			
59-0061			
59-0061	100.00 $\mu$ M	-17.890	
	31.25 $\mu$ M	-18.770	
	9.77 $\mu$ M	-17.170	
	3.05 $\mu$ M	-14.080	
	953.67 nM	-17.020	
	298.02 nM	-7.190	
	93.13 nM	-1.910	
	29.10 nM	-0.440	
	9.09 nM	-6.010	
	2.84 nM	-4.560	
			
59-0062			
59-0062	100.00 $\mu$ M	-13.940	
	31.25 $\mu$ M	-12.910	
	9.77 $\mu$ M	-4.560	
	3.05 $\mu$ M	-4.540	
	953.67 nM	-8.900	
	298.02 nM	-4.100	
	93.13 nM	-1.620	
	29.10 nM	3.230	

21/146

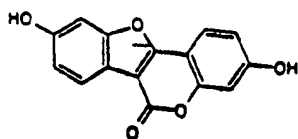
		9.09nM	8.070
		2.84nM	0.440
59-0063			
59-0063		100.00uM	-2.510
		31.25uM	-6.130
		9.77uM	-8.950
		3.05uM	-8.020
		953.67nM	-8.010
		298.02nM	-2.520
		93.13nM	-5.810
		29.10nM	-3.450
		9.09nM	-4.390
		2.84nM	-6.280
			
59-0064			
59-0064		100.00uM	-23.090
		31.25uM	-21.040
		9.77uM	78.400
		3.05uM	155.220
		953.67nM	113.120
		298.02nM	30.640
		93.13nM	15.240
		29.10nM	22.150
		9.09nM	-0.770
		2.84nM	4.410
			
59-0065			
59-0065		100.00uM	-2.030
		31.25uM	-2.980
		9.77uM	-15.240
		3.05uM	-15.400
		953.67nM	-15.240
		298.02nM	-10.520
		93.13nM	-13.830
		29.10nM	-5.810
		9.09nM	-3.620
		2.84nM	-7.070

22/146

			
59-0066			
59-0066	100.00 $\mu$ M	10.060	
	31.25 $\mu$ M	2.680	
	9.77 $\mu$ M	10.850	
	3.05 $\mu$ M	14.810	
	953.67 nM	0.950	
	298.02 nM	3.780	
	93.13 nM	1.730	
	29.10 nM	-2.820	
	9.09 nM	-2.820	
	2.84 nM	-3.920	
			
59-0067			
59-0067	100.00 $\mu$ M	-24.040	
	31.25 $\mu$ M	-24.690	
	9.77 $\mu$ M	-1.450	
	3.05 $\mu$ M	60.900	
	953.67 nM	133.860	
	298.02 nM	75.330	
	93.13 nM	28.760	
	29.10 nM	20.070	
	9.09 nM	4.980	
	2.84 nM	4.450	
			
59-0088			
59-0088	100.00 $\mu$ M	-22.130	
	31.25 $\mu$ M	-7.680	
	9.77 $\mu$ M	93.900	
	3.05 $\mu$ M	81.060	
	953.67 nM	22.330	
	298.02 nM	17.300	
	93.13 nM	8.480	
	29.10 nM	-3.530	
	9.09 nM	-4.230	
	2.84 nM	-6.140	



23/146



59-0069

59-0069

100.00  $\mu$ M

5.490

31.25  $\mu$ M

9.870

9.77  $\mu$ M

18.060

3.05  $\mu$ M

-7.180

953.67 nM

-2.840

298.02 nM

-3.710

93.13 nM

-11.180

29.10 nM

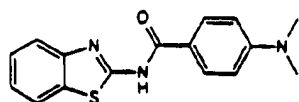
-5.790

9.09 nM

-7.180

2.84 nM

-4.750



59-0070

59-0070

100.00  $\mu$ M

-25.930

31.25  $\mu$ M

-23.000

9.77  $\mu$ M

36.060

3.05  $\mu$ M

214.280

953.67 nM

158.530

298.02 nM

72.890

93.13 nM

20.940

29.10 nM

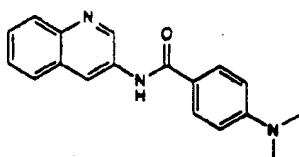
7.760

9.09 nM

7.590

2.84 nM

-8.400



59-0071

59-0071

100.00  $\mu$ M

-18.650

31.25  $\mu$ M

-15.540

9.77  $\mu$ M

17.060

3.05  $\mu$ M

176.090

953.67 nM

76.070

298.02 nM

31.260

93.13 nM

16.410

29.10 nM

4.870

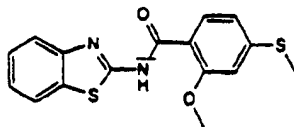
9.09 nM

-7.330

2.84 nM

-4.660

24/146



59-0072

59-0072

100.00  $\mu$ M -18.75031.25  $\mu$ M -18.6509.77  $\mu$ M -18.4303.05  $\mu$ M -15.770

953.67 nM 8.970

298.02 nM 74.740

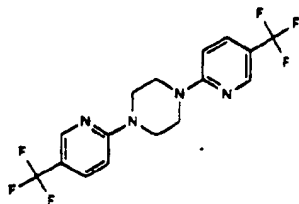
93.13 nM 175.430

29.10 nM 213.580

9.09 nM 164.320

2.84 nM 119.100

888.18 pM 60.770



59-0073

59-0073

100.00  $\mu$ M -3.01031.25  $\mu$ M -4.8309.77  $\mu$ M -9.6803.05  $\mu$ M -4.680

953.67 nM -6.500

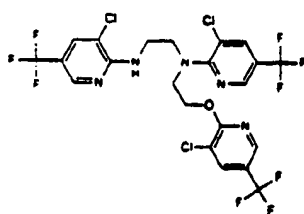
298.02 nM -2.510

93.13 nM 7.140

29.10 nM 0.97

9.09 nM -5.5

2.84 nM 5.3



59-0074

59-0074

100.00  $\mu$ M -2.8531.25  $\mu$ M 2.149.77  $\mu$ M -4.853.05  $\mu$ M -3.5

953.67 nM -4.65

298.02 nM 9.95

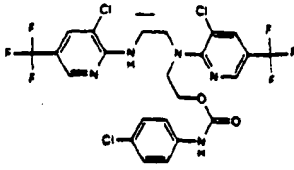
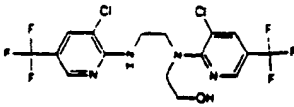
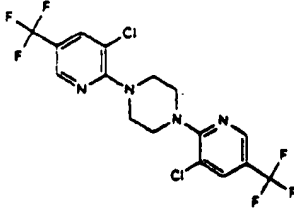
93.13 nM 4.47

29.10 nM -8

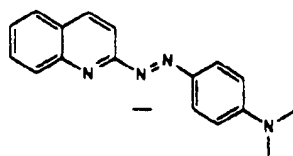
9.09 nM -4.17

2.84 nM 6.97

25/146

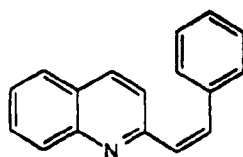
					
59-0075					
59-0075		100.00 $\mu$ M		-0.68	
		31.25 $\mu$ M		-10.16	
		9.77 $\mu$ M		-8.35	
		3.05 $\mu$ M		-6.51	
		953.67 nM		-0.85	
		298.02 nM		5.97	
		93.13 nM		0.97	
		29.10 nM		-2.35	
		9.09 nM		0.32	
		2.84 nM		10.47	
					
59-0076					
59-0076		100.00 $\mu$ M		-19.12	
		31.25 $\mu$ M		9.29	
		9.77 $\mu$ M		10.63	
		3.05 $\mu$ M		22.43	
		953.67 nM		19.93	
		298.02 nM		3.47	
		93.13 nM		19.93	
		29.10 nM		10.63	
		9.09 nM		14.28	
		2.84 nM		11.31	
					
59-0077					
59-0077		100.00 $\mu$ M		-20.96	
		31.25 $\mu$ M		-16.23	
		9.77 $\mu$ M		-10.58	
		3.05 $\mu$ M		-11.96	
		953.67 nM		-19.44	
		298.02 nM		-17.31	
		93.13 nM		-13.79	
		29.10 nM		-15.62	
		9.09 nM		-14.09	
		2.84 nM		-14.41	

26/146



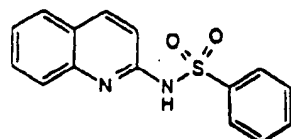
59-0078

100.00 $\mu$ M	-26.540
31.25 $\mu$ M	-22.560
9.77 $\mu$ M	71.530
3.05 $\mu$ M	207.960
953.67 nM	379.230
298.02 nM	241.460
93.13 nM	136.100
29.10 nM	84.020
9.09 nM	50.350
2.84 nM	56.600
0.80 nM	92.520



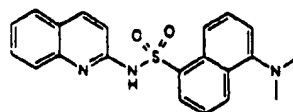
59-0079

100.00 $\mu$ M	-34.980
31.25 $\mu$ M	-21.390
9.77 $\mu$ M	37.200
3.05 $\mu$ M	122.580
953.67 nM	69.010
298.02 nM	64.000
93.13 nM	46.490
29.10 nM	30.310
9.09 nM	33.490
2.84 nM	29.760

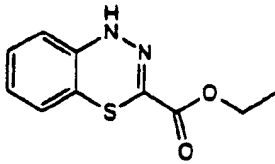
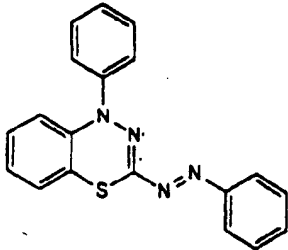
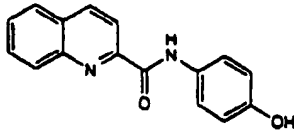


59-0080

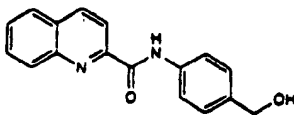
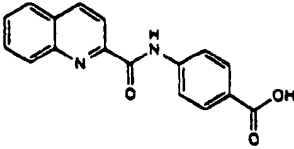
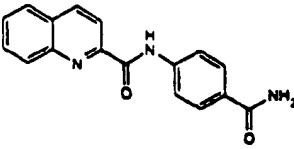
100.00 $\mu$ M	5.390
31.25 $\mu$ M	5.580
9.77 $\mu$ M	6.440
3.05 $\mu$ M	2.440
953.67 nM	-5.030
298.02 nM	7.660
93.13 nM	-3.630
29.10 nM	3.650
9.09 nM	1.050
2.84 nM	6.940

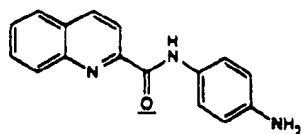


59-0081

59-0081	100.00 $\mu$ M	62.840
	31.25 $\mu$ M	11.300
	9.77 $\mu$ M	-8.670
	3.05 $\mu$ M	2.440
	953.67 nM	-5.200
	298.02 nM	-2.080
	93.13 nM	1.220
	29.10 nM	-2.250
	9.09 nM	1.050
	2.84 nM	-3.300
		
59-0082	100.00 $\mu$ M	111.79
59-0082	31.25 $\mu$ M	62.68
	9.77 $\mu$ M	32.38
	3.05 $\mu$ M	9.11
	953.67 nM	-10.62
	298.02 nM	-1.86
	93.13 nM	-6.89
	29.10 nM	-3.91
	9.09 nM	2.22
	2.84 nM	18.36
		
59-0083	100.00 $\mu$ M	48.93
59-0083	31.25 $\mu$ M	40.91
	9.77 $\mu$ M	25.85
	3.05 $\mu$ M	17.85
	953.67 nM	8.55
	298.02 nM	3.9
	93.13 nM	2.05
	29.10 nM	7.99
	9.09 nM	-3.91
	2.84 nM	3.35
		
59-0084	100.00 $\mu$ M	37.670
59-0084	31.25 $\mu$ M	26.050
	9.77 $\mu$ M	9.210
	3.05 $\mu$ M	10.070

28/146

		953.67 nM	21.700
		298.02 nM	5.900
		93.13 nM	4.870
		29.10 nM	-10.920
		9.09 nM	10.080
		2.84 nM	-2.080
 59-0085			
		100.00 uM	17.070
		31.25 uM	41.890
		9.77 uM	18.500
		3.05 uM	20.340
		953.67 nM	22.490
		298.02 nM	8.090
		93.13 nM	11.790
		29.10 nM	1.240
		9.09 nM	-0.780
 59-0086			
		100.00 uM	30.750
		31.25 uM	31.190
		9.77 uM	14.790
		3.05 uM	13.500
		953.67 nM	14.080
		298.02 nM	3.940
		93.13 nM	9.370
		29.10 nM	-2.610
		9.09 nM	-5.040
 59-0087			
		100.00 uM	10.880
		31.25 uM	11.080
		9.77 uM	3.100
		3.05 uM	-1.320
		953.67 nM	17.070
		298.02 nM	7.950
		93.13 nM	-4.480
		29.10 nM	4.510
		9.09 nM	-0.470
		2.84 nM	9.880



59-0088

59-0088

100.00  $\mu$ M31.25  $\mu$ M9.77  $\mu$ M3.05  $\mu$ M

953.67 nM

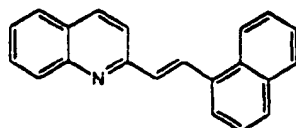
298.02 nM

93.13 nM

29.10 nM

9.09 nM

2.84 nM



59-0089

59-0089

100.00  $\mu$ M

60.09

31.25  $\mu$ M

118.25

9.77  $\mu$ M

65.84

3.05  $\mu$ M

36.1

953.67 nM

37.96

298.02 nM

18.42

93.13 nM

6.33

29.10 nM

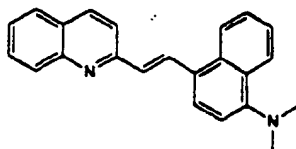
13.58

9.09 nM

0.75

2.84 nM

-5.77



59-0090

59-0090

100.00  $\mu$ M

32.77

31.25  $\mu$ M

24.63

9.77  $\mu$ M

19.5

3.05  $\mu$ M

41.31

953.67 nM

9.8

298.02 nM

-1.78

93.13 nM

3.53

29.10 nM

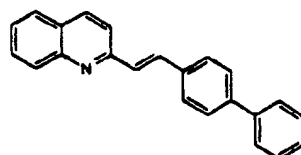
2.95

9.09 nM

2.95

2.84 nM

7.8



59-0091

59-0091

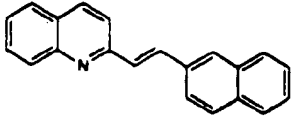
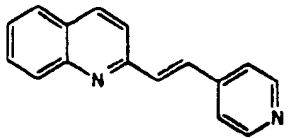
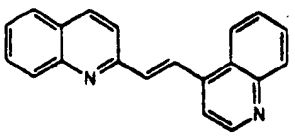
100.00  $\mu$ M

0.28

31.25  $\mu$ M

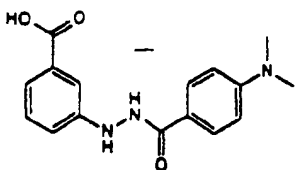
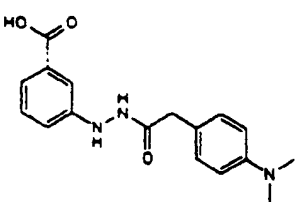
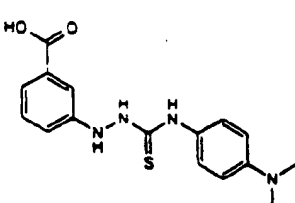
13.54

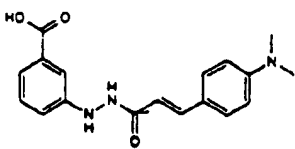
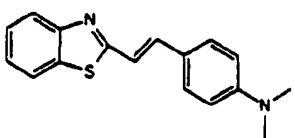
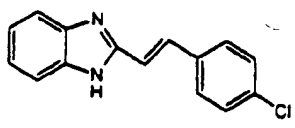
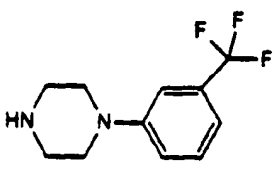
30/146

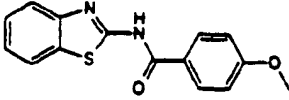
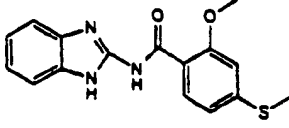
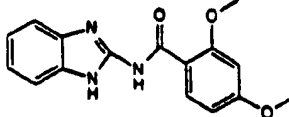
	9.77 $\mu$ M	95.94
	3.05 $\mu$ M	87.71
	953.67 nM	44.17
	298.02 nM	38.28
	93.13 nM	23.87
	29.10 nM	21.65
	9.09 nM	10.95
	2.84 nM	20.92
		
59-0092		
59-0092	100.00 $\mu$ M	-11.56
	31.25 $\mu$ M	17.84
	9.77 $\mu$ M	50.19
	3.05 $\mu$ M	25.84
	953.67 nM	14.41
	298.02 nM	6.77
	93.13 nM	8.62
	29.10 nM	2.22
	9.09 nM	8.38
	2.84 nM	1
		
59-0093		
59-0093	100.00 $\mu$ M	-11.67
	31.25 $\mu$ M	15.02
	9.77 $\mu$ M	35.44
	3.05 $\mu$ M	29.89
	953.67 nM	22.88
	298.02 nM	19.56
	93.13 nM	5.18
	29.10 nM	7.39
	9.09 nM	4.56
	2.84 nM	5.9
		
59-0094		
59-0094	100.00 $\mu$ M	-17.69
	31.25 $\mu$ M	45.15
	9.77 $\mu$ M	24.97
	3.05 $\mu$ M	19.81
	953.67 nM	9.35
	298.02 nM	1.38
	93.13 nM	9.24
	29.10 nM	-0.48
	9.09 nM	8.18
	2.84 nM	1.61



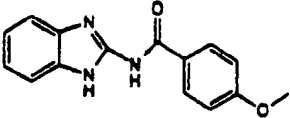
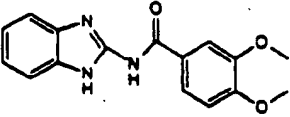
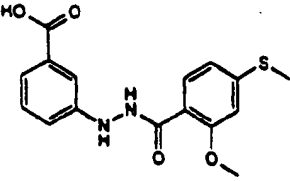
31/146

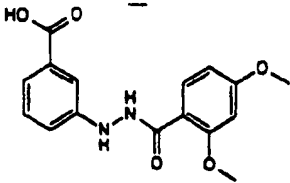
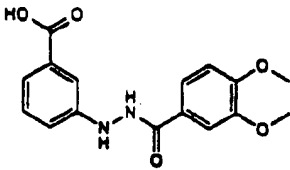
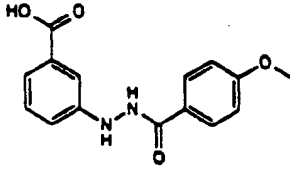
					
59-0095					
59-0095		100.00 $\mu$ M			44.7
		31.25 $\mu$ M			47.61
		9.77 $\mu$ M			12.78
		3.05 $\mu$ M			21.48
		953.67 nM			15.01
		298.02 nM			10.22
		93.13 nM			13.98
		29.10 nM			20.31
		9.09 nM			10.9
		2.84 nM			9.21
					
59-0096					
59-0096		100.00 $\mu$ M			413.05
		31.25 $\mu$ M			287.23
		9.77 $\mu$ M			137.38
		3.05 $\mu$ M			78.5
		953.67 nM			49.13
		298.02 nM			50.68
		93.13 nM			47.95
		29.10 nM			26.28
		9.09 nM			18.75
		2.84 nM			22.17
					
59-0097					
59-0097		100.00 $\mu$ M			77.47
		31.25 $\mu$ M			201.9
		9.77 $\mu$ M			160.93
		3.05 $\mu$ M			61.44
		953.67 nM			47.78
		298.02 nM			51.54
		93.13 nM			34.64
		29.10 nM			43.18
		9.09 nM			39.91
		2.84 nM			27.13

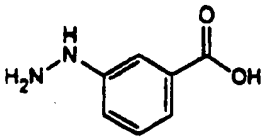
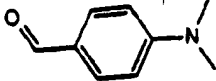
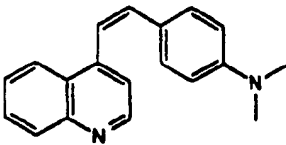
					
59-0098					
59-0098		100.00uM			-1.38
		31.25uM			186.89
		9.77uM			221.7
		3.05uM			164.69
		953.67nM			96.94
		298.02nM			68.25
		93.13nM			57
		29.10nM			51.88
		9.09nM			41.29
		2.84nM			33.43
					
59-0099					
59-0099		100.00uM		13.040	
		31.25uM		56.880	
		9.77uM		119.340	
		3.05uM		237.420	
		953.67nM		285.440	
		298.02nM		164.610	
		93.13nM		123.300	
		29.10nM		69.240	
		9.09nM		44.500	
		2.84nM		47.390	
					
59-0100					
59-0100		100.00uM		-10.020	
		31.25uM		-10.730	
		9.77uM		30.340	
		3.05uM		114.410	
		953.67nM		77.540	
		298.02nM		40.290	
		93.13nM		35.730	
		29.10nM		28.290	
		9.09nM		17.480	
		2.84nM		11.470	
					
59-0101					
59-0101		100.00uM		26.370	

		31.25 $\mu$ M	12.440
		9.77 $\mu$ M	-0.780
		3.05 $\mu$ M	10.280
		953.67 nM	2.110
		298.02 nM	7.860
		93.13 nM	1.140
		29.10 nM	2.820
		9.09 nM	4.150
		2.84 nM	5.990
			
58-0102	284.34		
58-0102		100.00 $\mu$ M	-24.350
		31.25 $\mu$ M	-11.140
		9.77 $\mu$ M	63.540
		3.05 $\mu$ M	121.320
		953.67 nM	79.530
		298.02 nM	72.460
		93.13 nM	66.290
		29.10 nM	45.690
		9.09 nM	27.260
		2.84 nM	42.330
		888.18 pM	33.430
			
59-0103	313.38		
		100.00 $\mu$ M	-29.69
		31.25 $\mu$ M	-29.53
		9.77 $\mu$ M	-28.22
		3.05 $\mu$ M	-27.72
		953.67 nM	-5.58
		298.02 nM	54.15
		93.13 nM	170.95
		29.10 nM	222.87
		9.09 nM	210.39
		2.84 nM	203.41
		0.80 nM	114.55
			
59-0104	297.31		
		100.00 $\mu$ M	-29.84
		31.25 $\mu$ M	-26.72
		9.77 $\mu$ M	-29.2
		3.05 $\mu$ M	-27.05
		953.67 nM	24.37
		298.02 nM	196.42
		93.13 nM	213.89

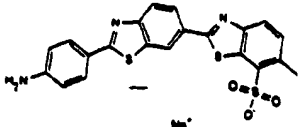
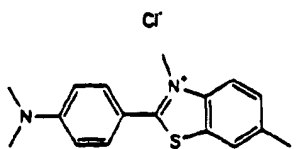
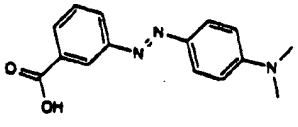
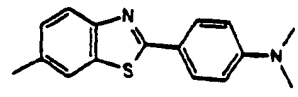
34/146

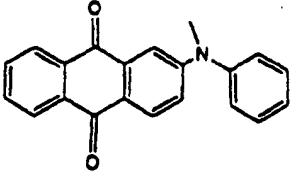
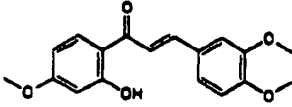
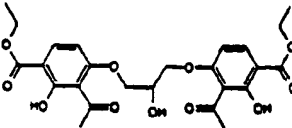
		29.10 nM	220.04
		9.09 nM	245.42
		2.84 nM	182.45
		0.80 nM	119.55
	267.29		
		100.00 uM	-25.72
		31.25 uM	-15.89
		9.77 uM	31.7
		3.05 uM	54.17
		953.67 nM	53.67
		298.02 nM	41.35
		93.13 nM	44.5
		29.10 nM	39.02
		9.09 nM	25.38
		2.84 nM	31.7
		0.80 nM	18.05
	297.31		
		100.00 uM	-14.05
		31.25 uM	223.52
		9.77 uM	202.58
		3.05 uM	107.73
		953.67 nM	71.3
		298.02 nM	44.84
		93.13 nM	26.54
		29.10 nM	23.05
		9.09 nM	27.67
		2.84 nM	12.23
		0.80 nM	11.4
	332.38		
		100.00 uM	48.55
		31.25 uM	22.67
		9.77 uM	7.18
		3.05 uM	0.65
		953.67 nM	11.12
		298.02 nM	-3.92
		93.13 nM	1.09
		29.10 nM	-15.69

		9.09 nM	1151.32
		2.84 nM	-2.62
		0.80 nM	-16.11
			
59-0108	316.31		
		100.00 uM	227.73
		31.25 uM	96.02
		9.77 uM	58.67
		3.05 uM	37.23
		953.67 nM	18.94
		298.02 nM	25.68
		93.13 nM	-4.8
		29.10 nM	2.62
		9.09 nM	-4.8
		2.84 nM	3.92
		0.80 nM	4.14
			
59-0109	316.31		
		100.00 uM	43.12
		31.25 uM	27.64
		9.77 uM	5.89
		3.05 uM	6.32
		953.67 nM	13.51
		298.02 nM	7.85
		93.13 nM	3.71
		29.10 nM	-3.27
		9.09 nM	5.01
		2.84 nM	-4.58
		0.80 nM	6.98
			
59-0110	266.29		
		100.00 uM	65.11
		31.25 uM	67.05
		9.77 uM	-35.27
		3.05 uM	25.26
		953.67 nM	27.01
		298.02 nM	15.24

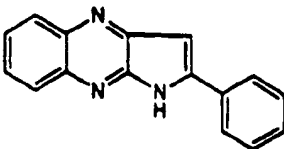
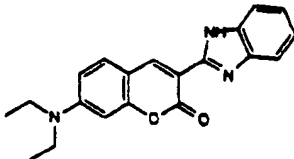
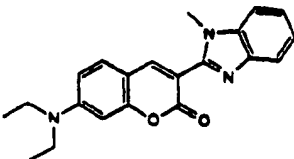
		93.13 nM	10.68
		29.10 nM	5.89
		9.09 nM	5.45
		2.84 nM	10.24
		0.80 nM	4.14
			
59-0111	152.15		
		100.00 uM	23.380
		31.25 uM	22.330
		9.77 uM	12.260
		3.05 uM	5.390
		953.67 nM	2.190
		298.02 nM	1.230
		93.13 nM	2.430
		29.10 nM	6.350
		9.09 nM	4.350
		2.84 nM	4.350
		0.80 nM	3.230
			
59-0112	149.19		
		100.00 uM	2.670
		31.25 uM	4.670
		9.77 uM	2.750
		3.05 uM	3.790
		953.67 nM	4.270
		298.02 nM	1.150
		93.13 nM	9.630
		29.10 nM	0.920
		9.09 nM	0.510
		2.84 nM	12.900
		0.80 nM	2.990
			
59-0113	274.37		
		100.00 uM	22.010
		31.25 uM	25.940
		9.77 uM	7.500
		3.05 uM	3.070
		953.67 nM	-0.760
		298.02 nM	-4.690
		93.13 nM	-4.790
		29.10 nM	5.090
		9.09 nM	0.150
		2.84 nM	-0.250
		0.80 nM	0.150

37/146

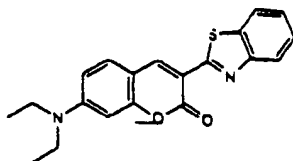
					
59-0114	475.54				
		100.00 $\mu$ M	52.030		
		31.25 $\mu$ M	36.120		
		9.77 $\mu$ M	25.840		
		3.05 $\mu$ M	16.670		
		953.67 nM	12.540		
		298.02 nM	9.420		
		93.13 nM	-1.060		
		29.10 nM	2.180		
		9.09 nM	-8.000		
		2.84 nM	2.470		
		0.80 nM	-1.480		
					
59-0115	318.87				
		100.00 $\mu$ M	73.700		
		31.25 $\mu$ M	2.770		
		9.77 $\mu$ M	-10.430		
		3.05 $\mu$ M	-12.340		
		953.67 nM	-13.760		
		298.02 nM	-13.980		
		93.13 nM	-11.940		
		29.10 nM	-9.830		
		9.09 nM	-8.820		
		2.84 nM	-0.950		
		0.80 nM	-0.050		
					
59-0116	269.30				
		100.00 $\mu$ M	31.380		
		31.25 $\mu$ M	109.080		
		9.77 $\mu$ M	231.070		
		3.05 $\mu$ M	240.670		
		953.67 nM	132.020		
		298.02 nM	75.820		
		93.13 nM	53.250		
		29.10 nM	47.500		
		9.09 nM	39.440		
		2.84 nM	42.170		
		0.80 nM	31.180		
					
59-0117	268.38				
		100.00 $\mu$ M	-68.520		

		31.25 $\mu$ M	39.450
		9.77 $\mu$ M	111.630
		3.05 $\mu$ M	64.340
		953.67 nM	4.740
		298.02 nM	-19.270
		93.13 nM	-26.660
		29.10 nM	-28.680
		9.09 nM	-42.180
		2.84 nM	-41.300
		0.80 nM	-39.220
			
59-0118	313.38		
		100.00 $\mu$ M	-57.170
		31.25 $\mu$ M	-56.580
		9.77 $\mu$ M	-56.060
		3.05 $\mu$ M	-55.720
		953.67 nM	-48.200
		298.02 nM	-50.300
		93.13 nM	-33.310
		29.10 nM	-47.340
		9.09 nM	-49.310
		2.84 nM	-56.200
		0.80 nM	-57.310
			
59-0119	314.34		
		100.00 $\mu$ M	167.500
		31.25 $\mu$ M	-29.240
		9.77 $\mu$ M	-57.800
		3.05 $\mu$ M	-52.030
		953.67 nM	-54.240
		298.02 nM	-53.870
		93.13 nM	-38.110
		29.10 nM	-55.100
		9.09 nM	-52.270
		2.84 nM	-53.500
		0.80 nM	-43.850
			
59-0120	504.49		
		100.00 $\mu$ M	-82.790
		31.25 $\mu$ M	-80.470
		9.77 $\mu$ M	-66.800
		3.05 $\mu$ M	-80.790
		953.67 nM	-54.240
		298.02 nM	-45.250
		93.13 nM	-50.660



		29.10nM	-50.300
		9.09nM	-50.300
		2.84nM	-50.300
		0.80nM	-43.280
 59-0121	245.29		
		100.00uM	-79.690
		31.25uM	-75.990
		9.77uM	25.650
		3.05uM	94.650
		953.67nM	43.910
		298.02nM	-1.800
		93.13nM	-4.150
		29.10nM	-22.050
		9.09nM	-31.110
		2.84nM	-26.760
		0.80nM	-28.270
 59-0122	333.39		
		100.00uM	-19.050
		31.25uM	-12.080
		9.77uM	-7.610
		3.05uM	25.210
		953.67nM	63.580
		298.02nM	67.220
		93.13nM	63.890
		29.10nM	42.680
		9.09nM	45.320
		2.84nM	37.780
		0.80nM	27.030
 59-0123	347.42		
		100.00uM	34.430
		31.25uM	34.710
		9.77uM	36.620
		3.05uM	55.100
		953.67nM	51.900
		298.02nM	41.410
		93.13nM	29.970
		29.10nM	13.760
		9.09nM	17.120
		2.84nM	13.480
		0.80nM	1.190

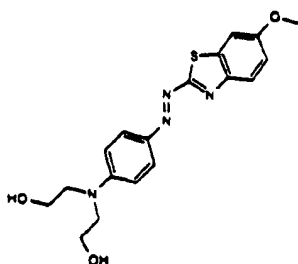
40/146



59-0124

350.44

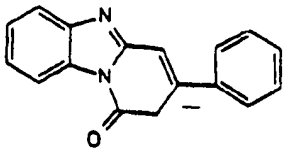
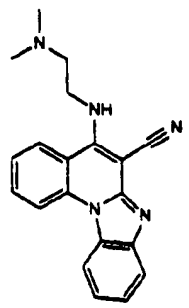
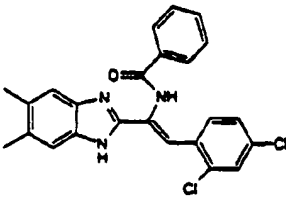
100.00 $\mu$ M	56.640
31.25 $\mu$ M	81.500
9.77 $\mu$ M	145.880
3.05 $\mu$ M	135.830
953.67 nM	288.990
298.02 nM	224.290
93.13 nM	134.850
29.10 nM	91.690
9.09 nM	80.390
2.84 nM	83.060
0.80 nM	51.460



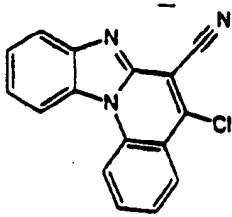
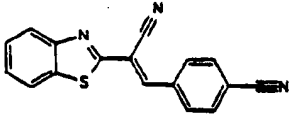
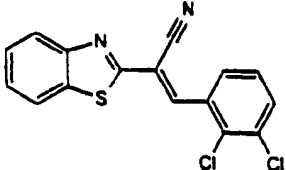
59-0125

372.45

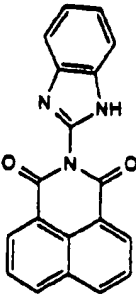
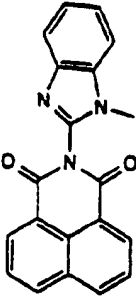
100.00 $\mu$ M	-6.780
31.25 $\mu$ M	67.530
9.77 $\mu$ M	54.120
3.05 $\mu$ M	28.700
953.67 nM	21.580
298.02 nM	22.280
93.13 nM	22.700
29.10 nM	1.830
9.09 nM	15.700
2.84 nM	9.840
0.80 nM	8.460

					
59-0126	260.30				
		100.00 $\mu$ M	-17.390		
		31.25 $\mu$ M	-13.100		
		9.77 $\mu$ M	9.270		
		3.05 $\mu$ M	40.530		
		953.67 nM	21.390		
		298.02 nM	25.660		
		93.13 nM	9.430		
		29.10 nM	6.360		
		9.09 nM	6.510		
		2.84 nM	0.080		
		0.80 nM	3.750		
					
59-0127	329.41				
		100.00 $\mu$ M	-20.610		
		31.25 $\mu$ M	-21.820		
		9.77 $\mu$ M	-6.060		
		3.05 $\mu$ M	-3.900		
		953.67 nM	-8.820		
		298.02 nM	-6.200		
		93.13 nM	11.880		
		29.10 nM	1.610		
		9.09 nM	3.600		
		2.84 nM	-2.070		
		0.80 nM	4.220		
					
59-0128	438.34				
		100.00 $\mu$ M			
		31.25 $\mu$ M			
		9.77 $\mu$ M			
		3.05 $\mu$ M			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			

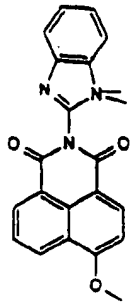
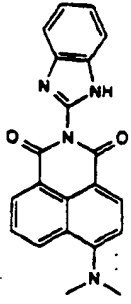
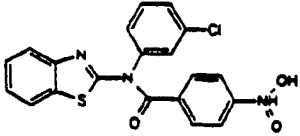
42/146

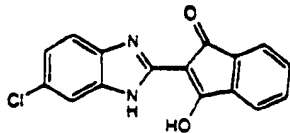
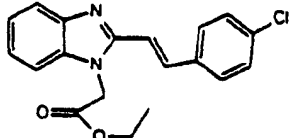
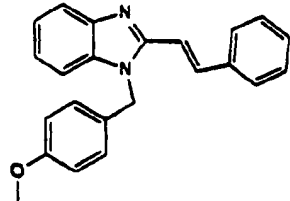
		2.84 nM				
		0.80 nM				
						
59-0129	277.71					
		100.00 uM	-20.48			
		31.25 uM	-21.21			
		9.77 uM	44.36			
		3.05 uM	4.38			
		953.67 nM	5.9			
		298.02 nM	3.8			
		93.13 nM	2.07			
		29.10 nM	4.22			
		9.09 nM	-0.68			
		2.84 nM	12.48			
		0.80 nM	-0.53			
						
59-0130	287.34					
		100.00 uM	4.38			
		31.25 uM	8.35			
		9.77 uM	5.91			
		3.05 uM	4.98			
		953.67 nM	0.39			
		298.02 nM	8.66			
		93.13 nM	2.85			
		29.10 nM	3.8			
		9.09 nM	4.36			
		2.84 nM	6.96			
		0.80 nM	24.75			
						
59-0131	331.22					
		100.00 uM	8.75			
		31.25 uM	0.12			
		9.77 uM	-10.38			
		3.05 uM	-6.39			
		953.67 nM	-2.81			
		298.02 nM	1.61			
		93.13 nM	-1.98			
		29.10 nM	-2.59			
		9.09 nM	0.14			
		2.84 nM	-5.77			

43/146

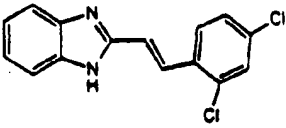
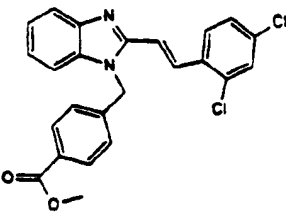
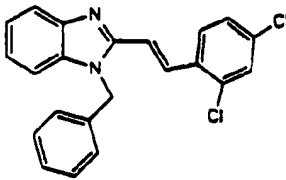
		0.80 nM	-0.51		
					
59-0132	313.32				
		100.00 uM	-17.11		
		31.25 uM	-14.81		
		9.77 uM	-14.37		
		3.05 uM	-12.92		
		953.67 nM	-13.54		
		298.02 nM	-10.38		
		93.13 nM	-3.65		
		29.10 nM	-7.66		
		9.09 nM	-6.18		
		2.84 nM	-9.97		
		0.80 nM	-2.81		
					
59-0133	327.34				
		100.00 uM	-16.04		
		31.25 uM	-16.91		
		9.77 uM	-17.31		
		3.05 uM	-16.71		
		953.67 nM	-9.34		
		298.02 nM	-12.69		
		93.13 nM	-11.23		
		29.10 nM	-17.74		
		9.09 nM	6.02		
		2.84 nM	-4.71		
		0.80 nM	0.55		

44/146

					
59-0134	357.37				
		100.00 $\mu$ M			
		31.25 $\mu$ M			
		9.77 $\mu$ M			
		3.05 $\mu$ M			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			
					
59-0135	358.39				
		100.00 $\mu$ M	-21.3		
		31.25 $\mu$ M	-14.16		
		9.77 $\mu$ M	-1.98		
		3.05 $\mu$ M	0.97		
		953.67 nM	11.68		
		298.02 nM	-1.13		
		93.13 nM	-1.55		
		29.10 nM	-2.81		
		9.09 nM	12.11		
		2.84 nM	-5.75		
		0.80 nM	4.54		
					
59-0136	411.87				
		100.00 $\mu$ M			
		31.25 $\mu$ M			
		9.77 $\mu$ M			
		3.05 $\mu$ M			
		953.67 nM			

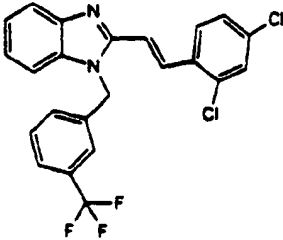
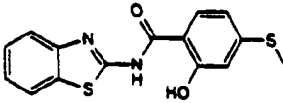
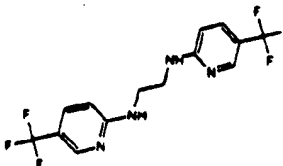
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			
					
59-0137	296.71				
		100.00 uM			
		31.25 uM			
		9.77 uM			
		3.05 uM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			
					
59-0138	340.81				
		100.00 uM	-6.91		
		31.25 uM	-12.68		
		9.77 uM	4.59		
		3.05 uM	32.61		
		953.67 nM	19.07		
		298.02 nM	8.18		
		93.13 nM	2.28		
		29.10 nM	12.22		
		9.09 nM	58.42		
		2.84 nM	7.24		
		0.80 nM	1.63		
					
59-0139	340.43				
		100.00 uM	45.93		
		31.25 uM	44.59		
		9.77 uM	53.62		
		3.05 uM	30.42		
		953.67 nM	26.25		
		298.02 nM	20.31		
		93.13 nM	18.81		

46 / 146

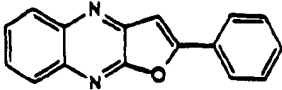
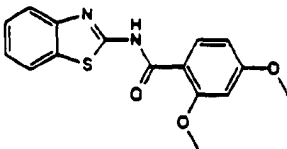
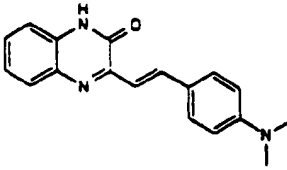
		29.10 nM	13.93
		9.09 nM	13.93
		2.84 nM	18.61
		0.80 nM	10.05
			
59-0140	289.17		
		100.00 uM	
		31.25 uM	
		9.77 uM	
		3.05 uM	
		953.67 nM	
		298.02 nM	
		93.13 nM	
		29.10 nM	
		9.09 nM	
		2.84 nM	
		0.80 nM	
			
59-0141	437.33		
		100.00 uM	-6.76
		31.25 uM	5.69
		9.77 uM	19.85
		3.05 uM	43.96
		953.67 nM	44.73
		298.02 nM	37.12
		93.13 nM	24.36
		29.10 nM	18.61
		9.09 nM	26.71
		2.84 nM	15.98
		0.80 nM	7.87
			
59-0142	378.29		
		100.00 uM	9.43
		31.25 uM	33.72
		9.77 uM	47.33
		3.05 uM	40.18
		953.67 nM	36.53
		298.02 nM	29.94
		93.13 nM	22.11



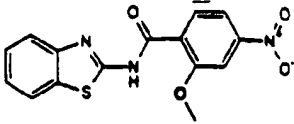
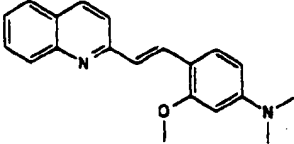
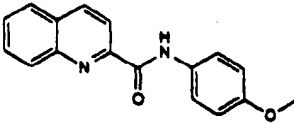
47/146

		200.0 nM	0.9
		9.09 nM	19.14
		2.84 nM	10.38
		0.80 nM	17.12
			
59-0143	447.29		
		100.00 uM	0.4
		31.25 uM	34.39
		9.77 uM	42.21
		3.05 uM	50.57
		953.67 nM	36.94
		298.02 nM	27.23
		93.13 nM	16.99
		29.10 nM	19.27
		9.09 nM	14.42
		2.84 nM	11.33
		0.80 nM	23.72
			
59-0144	316.40		
		100.00 uM	-14.59
		31.25 uM	-4.44
		9.77 uM	47.1
		3.05 uM	53.89
		953.67 nM	43.11
		298.02 nM	29.2
		93.13 nM	18.5
		29.10 nM	12.9
		9.09 nM	5.54
		2.84 nM	3.71
		0.80 nM	5.87
			
59-0145	350.27		
		100.00 uM	435.91
		31.25 uM	422.19
		9.77 uM	446.93
		3.05 uM	434.17
		953.67 nM	236.34
		298.02 nM	45.99
		93.13 nM	9.22
		29.10 nM	7.71
		9.09 nM	0.11

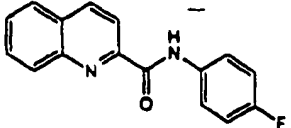
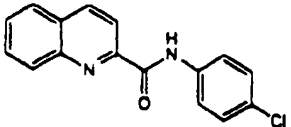
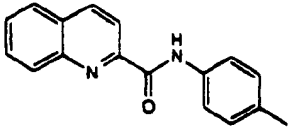
48/146

		2.84nM	6.27
		0.80nM	3.55
			
59-0146	246.27		
		100.00uM	-63.05
		31.25uM	4.42
		9.77uM	-13.73
		3.05uM	-16.48
		953.67nM	-35.47
		298.02nM	-51.25
		93.13nM	-50.13
		29.10nM	-42.92
		9.09nM	-45.64
		2.84nM	-56.56
		0.80nM	-39.68
			
59-0147	314.36		
		100.00uM	-85
		31.25uM	-85
		9.77uM	-80.29
		3.05uM	-41.67
		953.67nM	78.69
		298.02nM	269.13
		93.13nM	323.59
		29.10nM	339.88
		9.09nM	270.48
		2.84nM	245.58
		0.80nM	180.33
			
59-0148	291.35		
		100.00uM	-68.38
		31.25uM	-36.33
		9.77uM	-2.3
		3.05uM	12.12
		953.67nM	-2.42
		298.02nM	-16.21
		93.13nM	-30.87
		29.10nM	-35.58
		9.09nM	-39.07
		2.84nM	-41.18
		0.80nM	-45.53

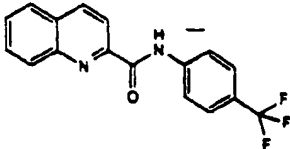
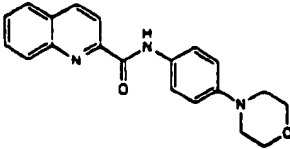
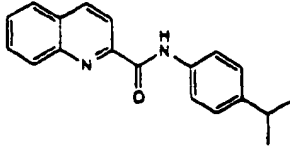
49/146

						
59-0149	329.33					
		100.00 $\mu$ M	-16.9			
		31.25 $\mu$ M	-1.8			
		9.77 $\mu$ M	-0.53			
		3.05 $\mu$ M	15.29			
		953.67 nM	78.78			
		298.02 nM	183.5			
		93.13 nM	223.57			
		29.10 nM	173.93			
		9.09 nM	122.3			
		2.84 nM	98.02			
		0.80 nM	69.06			
						
59-0150	304.39					
		100.00 $\mu$ M	63.32			
		31.25 $\mu$ M	193.53			
		9.77 $\mu$ M	419.26			
		3.05 $\mu$ M	497.21			
		953.67 nM	295.19			
		298.02 nM	193.35			
		93.13 nM	99.48			
		29.10 nM	69.96			
		9.09 nM	59			
		2.84 nM	52.16			
		0.80 nM	48.75			
						
59-0151	278.311					
59-0151		100.00 $\mu$ M	-6.660			
		31.25 $\mu$ M	18.240			
		9.77 $\mu$ M	18.300			
		3.05 $\mu$ M	11.690			
		953.67 nM	8.500			
		298.02 nM	9.070			
		93.13 nM	6.110			
		29.10 nM	5.880			
		9.09 nM	7.700			
		2.84 nM	2.000			
		0.80 nM	1.210			

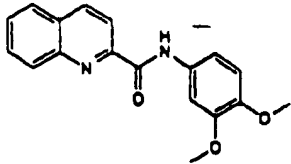
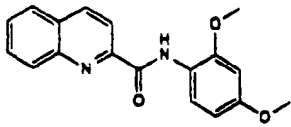
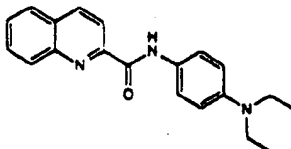
50/146

						
59-0152	266.275					
59-0152		100.00 $\mu$ M	-8.890			
		31.25 $\mu$ M	12.490			
		9.77 $\mu$ M	21.850			
		3.05 $\mu$ M	12.820			
		953.67 nM	7.330			
		298.02 nM	4.290			
		93.13 nM	9.750			
		29.10 nM	4.860			
		9.09 nM	1.320			
		2.84 nM	4.280			
		0.80 nM	4.160			
						
59-0153	282.73					
59-0153		100.00 $\mu$ M	-4.150			
		31.25 $\mu$ M	-0.390			
		9.77 $\mu$ M	11.120			
		3.05 $\mu$ M	14.540			
		953.67 nM	9.520			
		298.02 nM	11.570			
		93.13 nM	-0.160			
		29.10 nM	1.550			
		9.09 nM	-0.960			
		2.84 nM	4.730			
		0.80 nM	5.650			
						
59-0154	262.312					
59-0154		100.00 $\mu$ M	0.290			
		31.25 $\mu$ M	24.670			
		9.77 $\mu$ M	15.680			
		3.05 $\mu$ M	14.540			
		953.67 nM	13.170			
		298.02 nM	5.540			
		93.13 nM	2.690			
		29.10 nM	-1.190			
		9.09 nM	2.460			
		2.84 nM	4.170			
		0.80 nM	1.890			

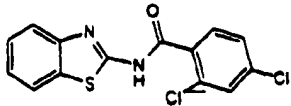
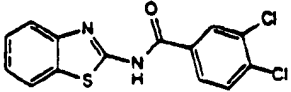
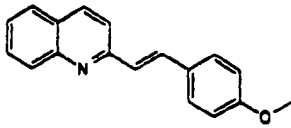
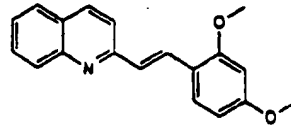
51/146

							
59-0155	316.282						
59-0155		100.00 $\mu$ M	-2.950				
		31.25 $\mu$ M	1.000				
		9.77 $\mu$ M	-9.450				
		3.05 $\mu$ M	-0.220				
		953.67 nM	0.690				
		298.02 nM	5.090				
		93.13 nM	-3.250				
		29.10 nM	0.530				
		9.09 nM	-1.900				
		2.84 nM	9.480				
		0.80 nM	-1.130				
							
59-0156	333.391						
59-0156		100.00 $\mu$ M	5.840				
		31.25 $\mu$ M	2.050				
		9.77 $\mu$ M	7.960				
		3.05 $\mu$ M	6.890				
		953.67 nM	-0.370				
		298.02 nM	-1.860				
		93.13 nM	-3.550				
		29.10 nM	-7.340				
		9.09 nM	-1.590				
		2.84 nM	2.650				
		0.80 nM	2.500				
							
59-0157	290.366						
59-0157		100.00 $\mu$ M	-6.440				
		31.25 $\mu$ M	14.920				
		9.77 $\mu$ M	19.930				
		3.05 $\mu$ M	11.440				
		953.67 nM	8.570				
		298.02 nM	-7.190				
		93.13 nM	0.080				
		29.10 nM	-0.230				
		9.09 nM	-4.460				
		2.84 nM	2.200				
		0.80 nM	9.920				

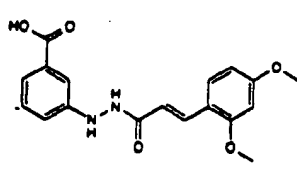
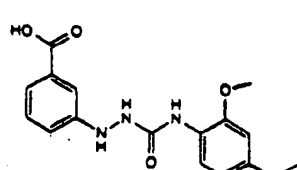
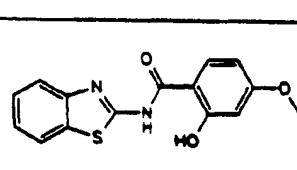
52/146

							
59-0158	308.337						
59-0158		100.00 $\mu$ M	-5.880				
		31.25 $\mu$ M	3.720				
		9.77 $\mu$ M	16.140				
		3.05 $\mu$ M	27.080				
		953.67 nM	9.930				
		298.02 nM	11.900				
		93.13 nM	2.810				
		29.10 nM	3.110				
		9.09 nM	0.690				
		2.84 nM	1.900				
		0.80 nM	7.970				
							
59-0159	308.337						
59-0159		100.00 $\mu$ M	2.790				
		31.25 $\mu$ M	13.530				
		9.77 $\mu$ M	4.700				
		3.05 $\mu$ M	10.910				
		953.67 nM	2.800				
		298.02 nM	9.710				
		93.13 nM	4.830				
		29.10 nM	0.650				
		9.09 nM	5.900				
		2.84 nM	6.610				
		0.80 nM	6.250				
							
59-0160	319.408						
59-0160		100.00 $\mu$ M	-5.060				
		31.25 $\mu$ M	-3.390				
		9.77 $\mu$ M	5.300				
		3.05 $\mu$ M	15.910				
		953.67 nM	6.610				
		298.02 nM	11.380				
		93.13 nM	4.460				
		29.10 nM	3.520				
		9.09 nM	4.700				
		2.84 nM	-0.650				
		0.80 nM	7.580				

53/146

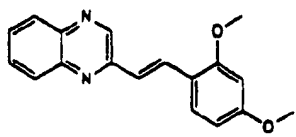
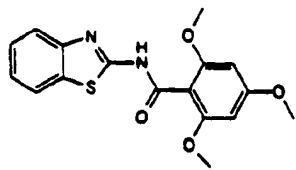
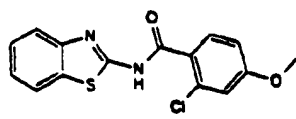
						
59-0196	323.201					
59-0196		100.00 $\mu$ M				
		31.25 $\mu$ M				
		9.77 $\mu$ M				
		3.05 $\mu$ M				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0197	323.201					
59-0197		100.00 $\mu$ M				
		31.25 $\mu$ M				
		9.77 $\mu$ M				
		3.05 $\mu$ M				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0198	261.324					
59-0198		100.00 $\mu$ M				
		31.25 $\mu$ M				
		9.77 $\mu$ M				
		3.05 $\mu$ M				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0199	291.35					
59-0199		100.00 $\mu$ M				
		31.25 $\mu$ M				

54 / 146

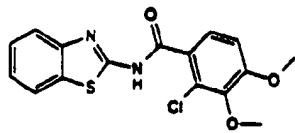
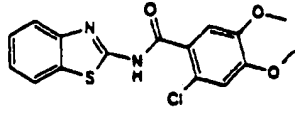
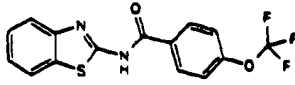
		Δ <sub>max</sub> μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0200	342.351					
59-0200		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0201	331.328					
59-0201		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0202	300.336					
59-0202		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				



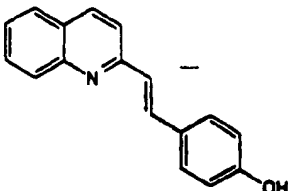
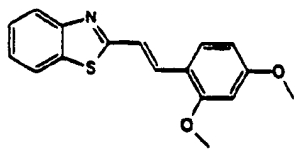
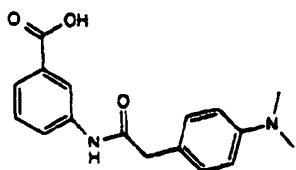
55 / 146

		9.09nM				
		2.84nM				
		0.80nM				
						
59-0203	292.338					
59-0203		100.00uM				
		31.25uM				
		9.77uM				
		3.05uM				
		953.67nM				
		298.02nM				
		93.13nM				
		29.10nM				
		9.09nM				
		2.84nM				
		0.80nM				
						
59-0204	344.389					
59-0204		100.00uM				
		31.25uM				
		9.77uM				
		3.05uM				
		953.67nM				
		298.02nM				
		93.13nM				
		29.10nM				
		9.09nM				
		2.84nM				
		0.80nM				
						
59-0205	318.782					
59-0205		100.00uM				
		31.25uM				
		9.77uM				
		3.05uM				
		953.67nM				
		298.02nM				
		93.13nM				
		29.10nM				
		9.09nM				
		2.84nM				
		0.80nM				

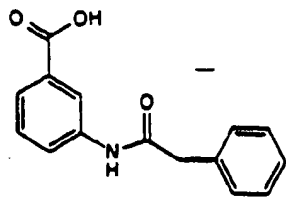
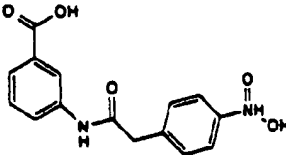
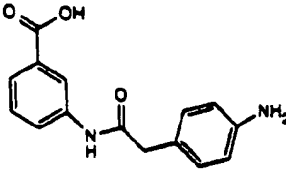
56/146

						
59-0206	348.808					
59-0206		100.00 uM				
		31.25 uM				
		9.77 uM				
		3.05 uM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0207	348.808					
59-0207		100.00 uM				
		31.25 uM				
		9.77 uM				
		3.05 uM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0208	338.307					
59-0208		100.00 uM				
		31.25 uM				
		9.77 uM				
		3.05 uM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				

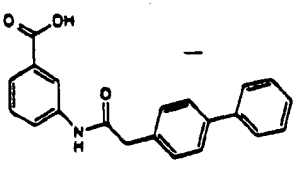
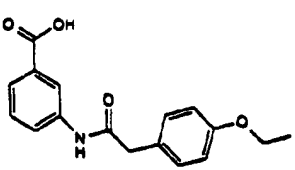
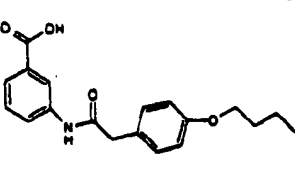
57/146

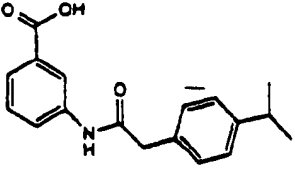
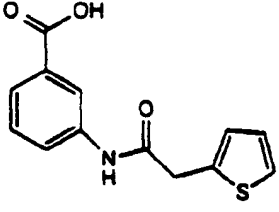
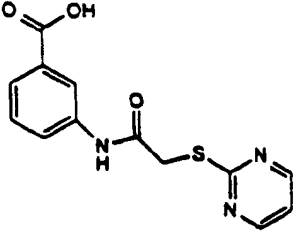
							
59-0209	247.287						
59-0209		100.00	uM				
		31.25	uM				
		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				
							
59-0210	297.376						
59-0210		100.00	uM				
		31.25	uM				
		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				
							
59-8000	298.342						
59-8000		100.00	uM				
		31.25	uM				
		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				

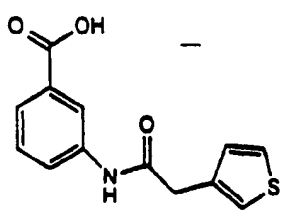
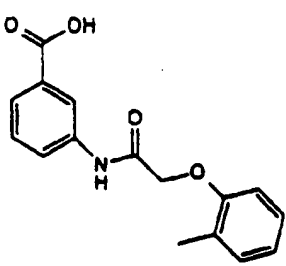
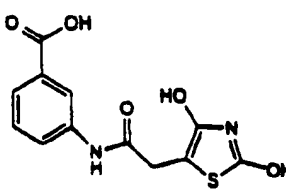
58/146

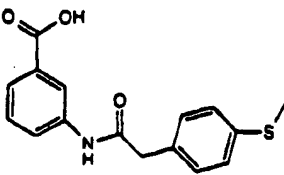
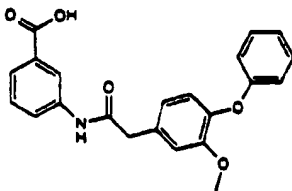
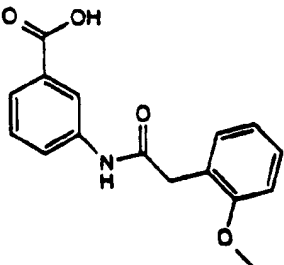
						
59-8001	255.273					
59-8001		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
						
59-8002	302.286					
59-8002		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
						
59-8003	270.288					
59-8003		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			

59 / 146

							
59-8004	331.371						
59-8004		100.00	uM				
		31.25	uM				
		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				
							
59-8005	299.326						
59-8005		100.00	uM				
		31.25	uM				
		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				
							
59-8006	327.38						
59-8006		100.00	uM				
		31.25	uM				
		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				

						
59-8007	297.354					
59-8007		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
						
59-8008	261.299					
59-8008		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
						
59-8009	289.313					
59-8009		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			

		2.55 nM	0.80 nM				
							
59-8010	281.299						
59-8010		100.00 uM					
		31.25 uM					
		9.77 uM					
		3.05 uM					
		953.67 nM					
		298.02 nM					
		93.13 nM					
		29.10 nM					
		9.09 nM					
		2.84 nM					
		0.80 nM					
							
59-8011	283.299						
59-8011		100.00 uM					
		31.25 uM					
		9.77 uM					
		3.05 uM					
		953.67 nM					
		298.02 nM					
		93.13 nM					
		29.10 nM					
		9.09 nM					
		2.84 nM					
		0.80 nM					
							
59-8012	284.285						
59-8012		100.00 uM					
		31.25 uM					
		9.77 uM					
		3.05 uM					
		953.67 nM					
		298.02 nM					

		59XLS nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-8013	301.364					
59-8013		100.00 uM				
		31.25 uM				
		9.77 uM				
		3.05 uM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-8014	377.398					
59-8014		100.00 uM				
		31.25 uM				
		9.77 uM				
		3.05 uM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-8015	285.299					
59-8015		100.00 uM				
		31.25 uM				
		9.77 uM				
		3.05 uM				





64/146

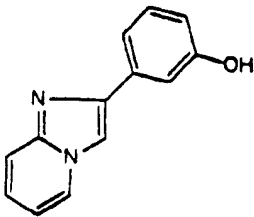
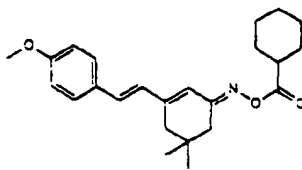
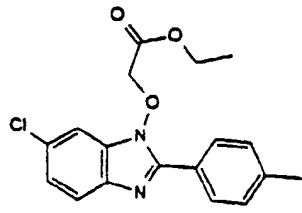
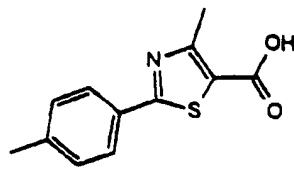
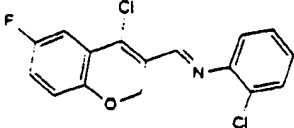
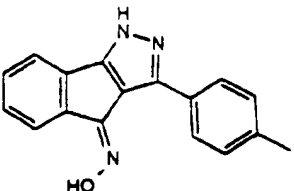
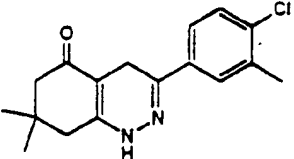
CHEMISTRY	Concentration	ABA-S
 51-2229		
	100.00 $\mu$ M	125.320
	10.00	28.260
	210.236	20.140
	2.00	-9.740
	0.40	-9.710
 92-3052		
	131.056 $\mu$ M	-9.28
	13.108	113.80
	381.516	12.81
	0.524	20.25
	0.105	24.45
 92-3390		
	145.012 $\mu$ M	-8.05
	14.501	31.57
	344.798	139.66
	0.580	49.82
	0.118	21.01
 92-3552		
	214.326 $\mu$ M	108.15

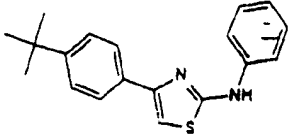
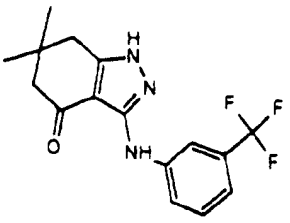
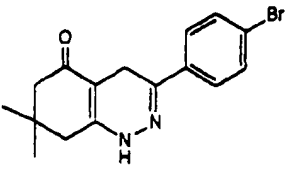
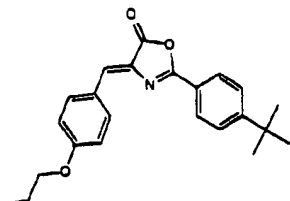
Figure 4

4-1

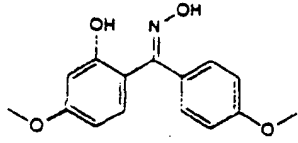
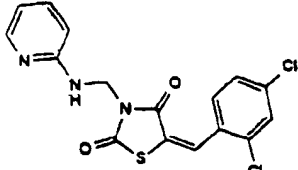
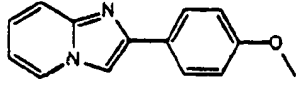
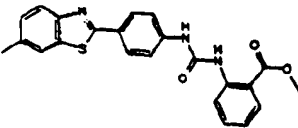
65/146

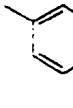
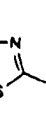
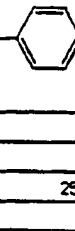
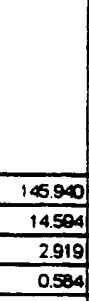
	21.433		69.74
233.289	4.287		31.59
	0.857		39.70
	0.171		18.29
			
92-6353			
92-6353	155.199	uM	
	31.040		204.14
322.166	15.520		154.94
	3.104		28.09
	1.552		
	0.310		3.53
			
92-8007			
92-8007	181.813	uM	-18.65
	36.323		58.65
275.311	18.181		142.33
	3.632		45.65
	1.816		
	0.363		4.47
			
92-8215			
92-8215	165.123	uM	32.90
	33.025		151.08
302.805	18.512		132.29
	3.302		59.90
	1.651		
	0.330		23.34

66 / 146

			
92-8258			
92-8258	162.102	uM	-16.65
	32.420		157.44
	308.447	18.210	101.04
		3.242	39.02
		1.621	
		0.324	12.78
			
92-8362			
92-8362	154.647	uM	138.79
	30.929		137.00
	323.318	15.465	65.02
		3.083	17.34
		1.546	
		0.308	0.41
			
92-8372			
92-8372	150.045	uM	83.78
	30.009		134.71
	333.234	15.004	92.08
		3.001	31.35
		1.500	
		0.300	13.20
			
92-9183			

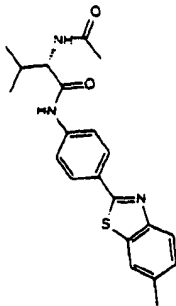
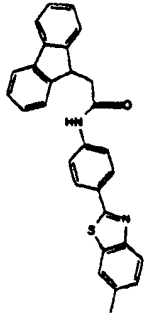
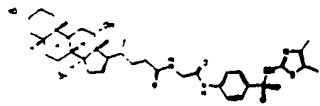
67/146

92-9183	137.568 $\mu$ M	-22.80
	13.757	16.61
363.457	2.751	101.96
	1.376	
	0.550	58.17
	0.110	38.47
		
93-0215		
93-0215	182.957 $\mu$ M	115.230
	18.296	88.110
273.288	3.659	20.870
	0.732	-28.680
	0.146	5.250
		
93-0399		
93-0399	131.491 $\mu$ M	128.130
	13.149	38.560
380.253	2.630	41.240
	0.528	-4.910
	0.105	3.910
		
93-0587		
93-0587	222.953 $\mu$ M	178.130
	22.295	60.410
224.263	4.459	-0.180
	0.892	-3.470
	0.178	-8.460
		
93-1327		
93-1327	119.764 $\mu$ M	-42.000
	11.978	119.130
417.487	2.395	67.930
	0.479	8.520

	0.096	
		
93-1340		
93-1340	196.576	uM
	19.658	
	254.355	3.932
		0.786
		0.157
		
93-1474		
93-1474	145.940	uM
	14.594	
	342.607	2.919
		0.584
		0.117
		
93-1766		
93-1766	144.348	uM
	14.435	
	346.398	2.887
		0.577
		0.115
		
93-1866		
93-1866	148.214	uM
	14.821	

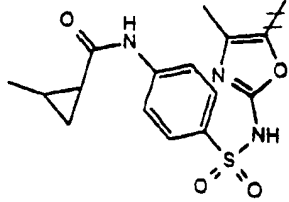
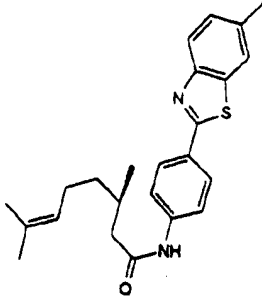
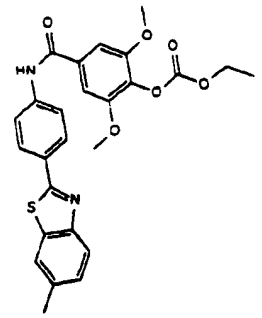
[illegible]

69 / 146

337.349	2.964	
--	0.593	
	0.119	
		
850-7377		
850-7377	131.052 $\mu$ M	
	13.108	
381.488	2.621	
	0.524	
	0.105	
		
850-7413		
850-7413	111.954 $\mu$ M	
	11.196	
448.572	2.239	
	0.448	
	0.090	
		
850-7449		
850-7449	69.938 $\mu$ M	
	6.994	
714.923	1.398	
	0.280	
	0.058	

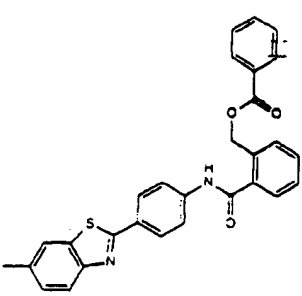
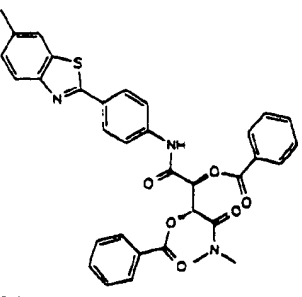
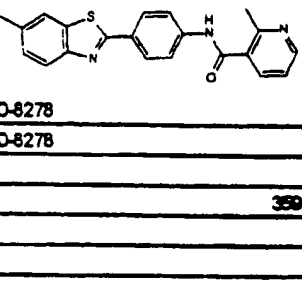
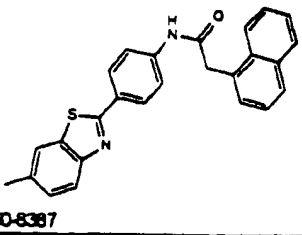
2.600
-7.350
-25.160
-50.32
68.27
118.61
61.26
35.86
-40.44
-2.55
157.01
78.73
23.91
-42.42
73.79
112.18
75.24
28.38

70/146

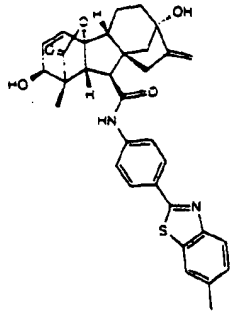
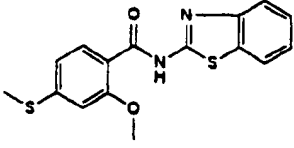
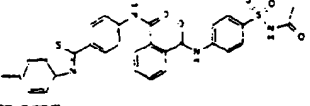
				
850-7485				
850-7485		143.099	μM	-42.91
		14.310		28.36
	349.409	2.862		153.04
		0.572		74.27
		0.114		50.28
				
850-7991				
850-7991		127.367	μM	-16.87
		12.737		8.95
	392.565	2.547		105.51
		0.508		47.53
		0.102		54.28
				
850-8170				
850-8170		101.513	μM	-33.79
		10.151		158.65
	492.55	2.030		128.27
		0.408		43.05
		0.081		50.00



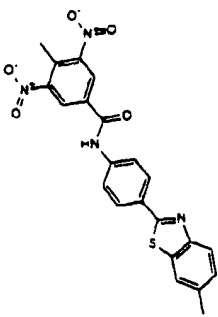
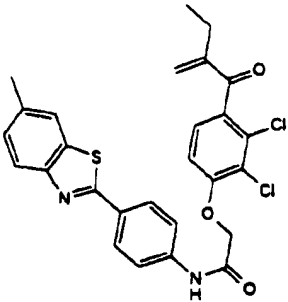
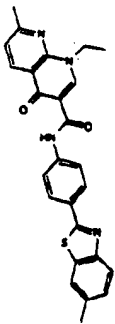
71 / 146

			
850-8205			
850-8205	104.478	uM	-39.52
	10.448		51.18
478.57	2.090		163.82
	0.418		108.06
	0.084		73.68
CHIRAL			
			
850-8241			
850-8241	82.279	uM	-2.07
	8.228		181.77
607.695	1.648		118.23
	0.329		88.73
	0.088		38.14
			
850-8278			
850-8278	139.101	uM	-40.08
	13.910		39.00
359.451	2.782		182.38
	0.558		122.84
	0.111		78.90
			
850-8387			

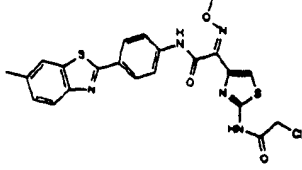
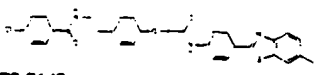
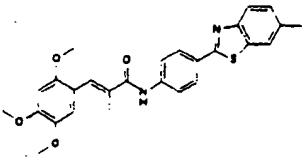
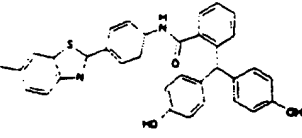
72/146

850-8387	122.392	$\mu\text{M}$	-17.06
	12.239		130.31
408.523	2.448		129.75
	0.480		62.69
	0.098		40.74
			
850-8469			
850-8469	87.921	$\mu\text{M}$	-21.13
	8.792		11.30
568.692	1.758		131.92
	0.352		71.13
	0.070		58.95
			
850-8613			
850-8613	151.319	$\mu\text{M}$	-28.05
	15.132		85.95
330.428	3.028		381.37
	0.605		256.32
	0.121		122.93
			
850-8637			
850-8637	85.518	$\mu\text{M}$	-25.17
	8.552		33.35
584.673	1.710		122.49
	0.342		57.19
	0.088		37.42

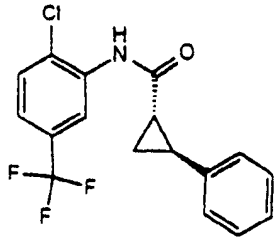
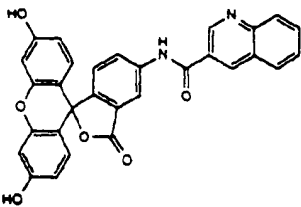
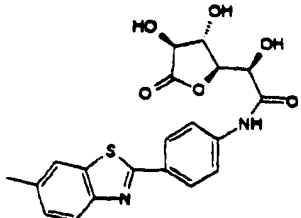
73 / 146

			
850-8889			
850-8889	111.493	uM	-17.470
	11.149		142.970
448.457	2.230		74.150
	0.446		21.010
	0.089		8.530
			
850-8964			
850-8964	95.158	uM	-30.92
	9.518		44.98
525.454	1.903		128.29
	0.381		49.84
	0.076		44.99
			
850-9071			
850-9071	109.998	uM	-24.620
	11.000		64.120
454.552	2.200		148.030
	0.440		54.540

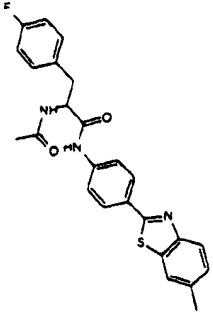
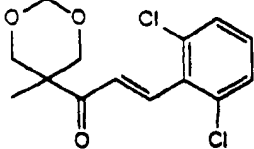
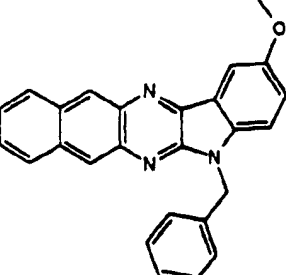
74/146

	0.088		23.540
			
850-9106			
850-9106	100.000	uM	-15.710
	10.000		99.820
	499.999	2.000	111.960
		0.400	74.500
		0.080	23.150
			
850-9142			
850-9142	85.596	uM	-14.980
	8.580		165.770
	584.138	1.712	66.650
		0.342	27.780
		0.068	0.670
			
850-9179			
850-9179	105.357	uM	-24.630
	10.538		105.200
	474.579	2.107	89.280
		0.421	48.110
		0.084	19.180
			
850-9212			
850-9212	92.139	uM	-28.580
	9.214		40.900
	542.657	1.843	111.690
		0.389	78.950
		0.074	30.840

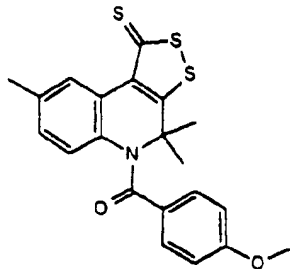
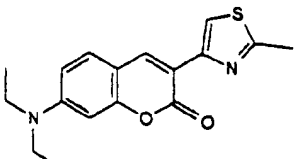
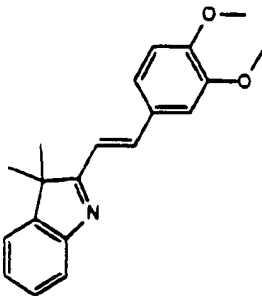
75/146

					
850-9287					
850-9287			147.170	uM	-15.82
			14.717		15.82
339.744			2.943		130.71
			0.589		91.11
			0.118		69.05
					
850-9356					
850-9356			99.506	uM	-24.660
			9.951		83.140
502.482			1.960		168.810
			0.398		45.470
			0.080		9.740
					
850-9467					
850-9467			120.648	uM	-19.800
			12.065		112.980
414.438			2.413		122.730
			0.483		43.520
			0.097		33.140

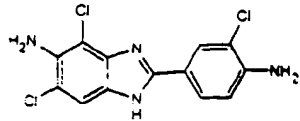
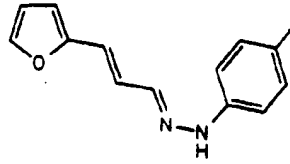
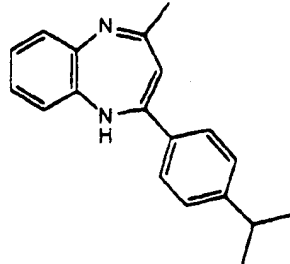
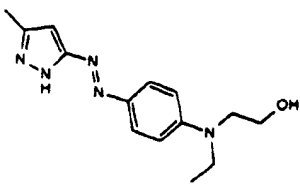
76/146

			
850-9576			
850-9576	111.724	uM	
	11.172		-27.430
	447.532	2.234	90.560
		0.447	101.610
		0.089	44.900
			19.930
			
895-0262			
895-0262	166.019	uM	
	33.204		-19.18
	301.169	16.602	-12.60
		3.320	146.28
		0.332	-2.23
			-3.07
			
895-0268			
895-0268	126.363	uM	
	25.677		-18.87
	369.468	12.636	40.25
		2.568	169.96
		0.257	195.29
			14.02

77/146

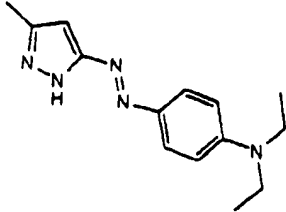
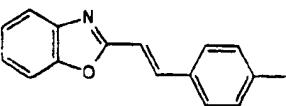
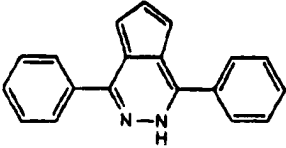
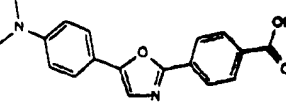
				
895-0594				
895-0594	120.896	uM		-21.63
	12.090			25.89
	413.58	2.418		122.10
		0.484		75.32
		0.097		39.42
				
895-0857				
895-0857	159.028	uM		-30.48
	15.903			148.74
	314.407	3.181		74.54
		0.638		25.82
		0.127		3.68
				
895-0984				
895-0984	182.655	uM		-31.08
	18.265			325.08
	307.393	3.253		87.51
		0.851		40.38
		0.130		18.03

78/146

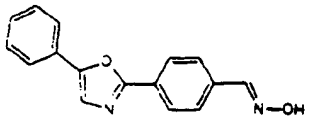
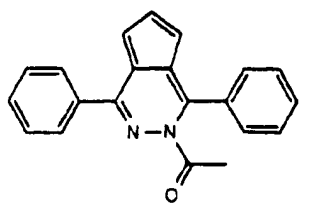
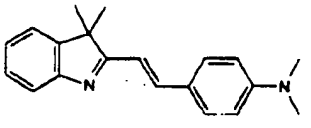
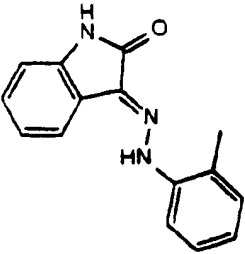
			
895-1161			
895-1161	152.625	uM	-5.51
	15.263		109.31
327.602	3.053		56.06
	0.611		29.49
	0.122		24.71
			
895-1420			
895-1420	220.965	uM	-19.47
	22.097		110.90
226.279	4.419		49.94
	0.884		33.65
	0.177		20.08
			
895-1679			
895-1679	180.810	uM	-30.36
	18.091		111.72
276.383	3.618		102.83
	0.724		18.01
	0.145		0.44
			
895-1691			
895-1691	182.922	uM	-18.29
	18.292		50.84
273.34	3.658		105.70



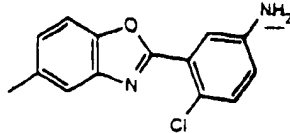
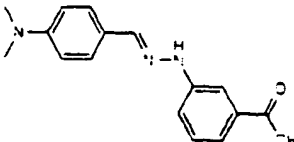
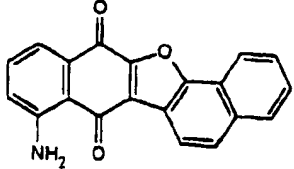
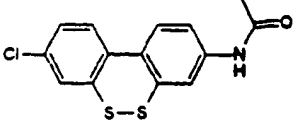
79/146

	0.732		60.23
	0.146		23.42
			
895-1754			
895-1754	194.295	uM	-31.44
	19.430		132.78
257.341	3.886		75.39
	0.777		39.30
	0.155		16.19
			
895-1888			
895-1888	212.504	uM	-33.65
	21.250		29.75
235.286	4.250		148.84
	0.850		73.77
	0.170		28.14
			
895-2474			
895-2474	184.952	uM	-20.74
	18.405		128.69
270.335	3.699		68.37
	0.740		43.27
	0.148		19.44
			
895-2475			
895-2475	162.159	uM	265.41
	16.216		287.88
308.337	3.243		227.34
	0.648		65.40
	0.130		28.96

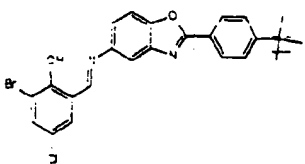
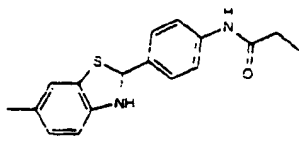
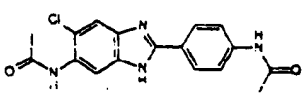
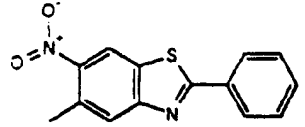
80/146

			
895-2544			
895-2544	189.186	uM	17.53
	18.919		136.50
254.284	3.784		59.15
	0.757		24.75
	0.151		11.86
			
895-3113			
895-3113	180.067	uM	-22.22
	18.007		224.52
312.372	3.201		68.48
	0.640		43.36
	0.128		30.56
			
895-3306			
895-3306	172.170	uM	-23.24
	17.217		38.63
290.41	3.443		333.10
	0.689		164.63
	0.138		64.33
			
895-3810			
895-3810	198.973	uM	89.79
	19.897		108.75
251.289	3.979		73.78
	0.796		33.45
	0.159		16.86

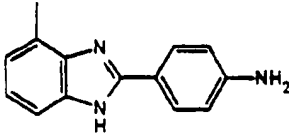
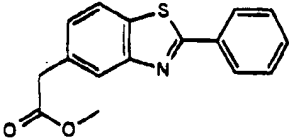
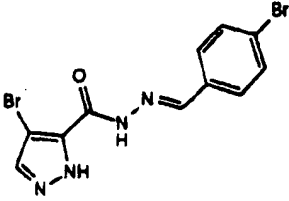
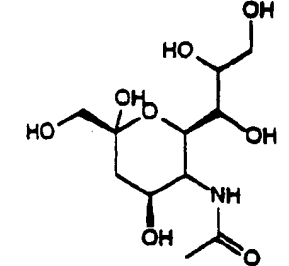
81/146

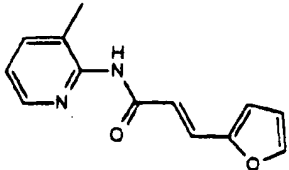
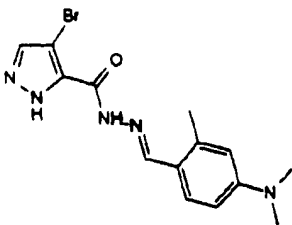
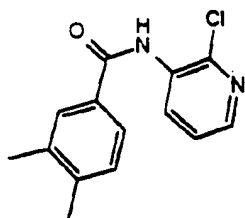
			
895-3846			
895-3846	193.267	uM	-21.41
	19.327		13.40
258.708	3.865		114.46
	0.773		52.12
	0.155		38.29
			
895-4642			
895-4642	176.473	uM	6.97
	17.647		283.99
283.331	3.529		447.51
	0.706		304.86
	0.141		100.46
			
895-4843			
895-4843	159.581	uM	-17.18
	15.958		24.54
313.312	3.192		100.12
	0.638		60.37
	0.128		27.85
			
895-5185			
895-5185	182.433	uM	-6.47
	18.243		213.42
307.821	3.249		107.83
	0.650		48.75
	0.130		18.27

82 / 146

			
895-5960			
895-5960	103.348	uM	-10.03
	10.335		158.04
483.798	2.067		62.07
	0.413		34.47
	0.083		7.24
			
895-6353			
895-6353	167.555	uM	-10.45
	16.755		21.59
298.408	3.351		101.77
	0.670		54.91
	0.134		24.15
			
895-6643			
895-6643	145.862	uM	100.09
	14.586		74.25
342.786	2.917		16.86
	0.583		-0.89
	0.117		-7.94
			
895-7828			
895-7828	184.973	uM	-32.44
	18.497		-29.24
270.31	3.699		85.15
	0.740		125.64
	0.148		-30.80

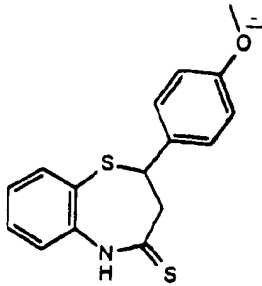
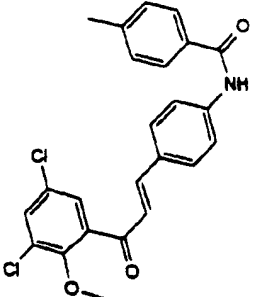
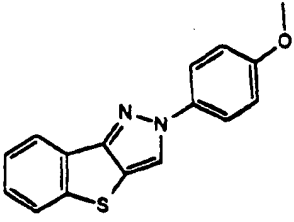
83/146

			
895-7985			
895-7985	223.935	uM	122.070
	22.394		3.900
	223.279	4.479	-7.790
	0.898		5.520
	0.179		-2.270
			
895-7997			
895-7997	176.461	uM	
	17.648		
	283.349	3.529	
	0.708		
	0.141		
			
895-8053			
895-8053	134.308	uM	
	13.440		
	372.03	2.686	
	0.538		
	0.108		
			
895-8137			
895-8137	189.326	uM	

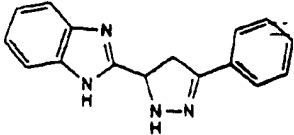
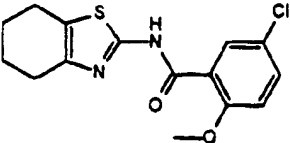
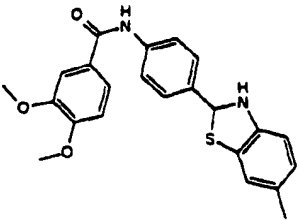
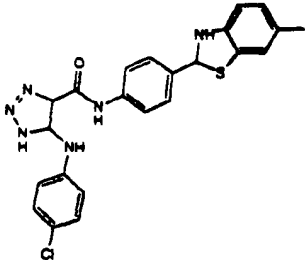
		16.933	
	295.268	3.367	
		0.677	
		0.135	
			
895-8185			
895-8185		219.057	uM
		21.906	
	228.251	4.381	
		0.876	
		0.175	
			
895-8286			
895-8286		142.785	uM
		14.277	
	350.225	2.855	
		0.571	
		0.114	
			
895-8383			
895-8383		191.774	uM
		18.177	
	280.724	3.635	
		0.787	
		0.153	

[illegible]

85/146

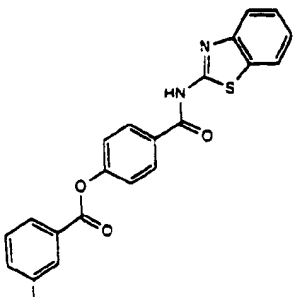
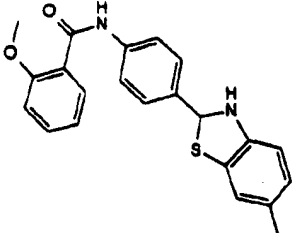
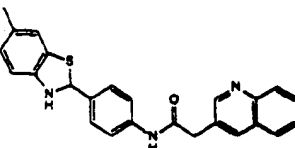
					
895-8862					
895-8862	165.878	$\mu\text{M}$		54.72	
	16.588			159.21	
	301.43	3.318		113.97	
		0.664		41.96	
		0.133		38.28	
					
895-8863					
895-8863	113.552	$\mu\text{M}$		-21.87	
	11.355			201.56	
	440.328	2.271		12.55	
		0.454		0.62	
		0.091		-0.69	
					
895-8868					
895-8868	178.349	$\mu\text{M}$		-29.16	
	17.835			0.62	
	280.349	3.567		182.84	
		0.713		118.55	
		0.143		42.75	

86/146

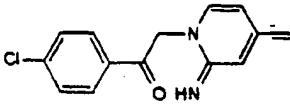
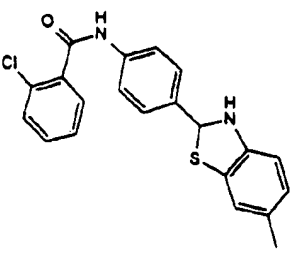
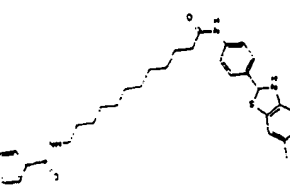
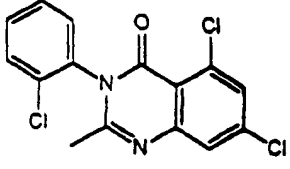
			
896-0122			
896-0122	190.610	uM	-14.15
	19.061		151.42
262.316	3.812		56.90
	0.762		19.20
	0.152		11.42
			
896-0246			
896-0246	154.898	uM	-17.57
	15.489		34.35
322.814	3.098		102.03
	0.620		48.52
	0.124		20.52
			
896-0255			
896-0255	123.000	uM	-17.14
	12.300		67.75
408.504	2.460		108.78
	0.482		61.27
	0.096		48.97
			
896-0345			
896-0345	107.532	uM	-18.88
	10.753		77.80



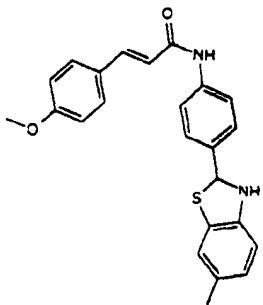
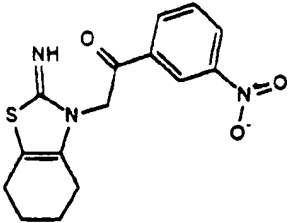
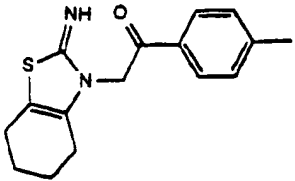
87/146

	464.979	2.151		188.94
		0.430		106.12
		0.086		37.18
				
896-0390				
896-0390		128.718 $\mu\text{M}$		-16.90
		12.872		87.23
	388.445	2.574		210.25
		0.515		73.35
		0.103		28.25
				
896-0535				
896-0535		132.810 $\mu\text{M}$		-10.41
		13.281		73.84
	376.478	2.658		199.80
		0.531		102.12
		0.106		35.72
				
896-0554				
896-0554		121.489 $\mu\text{M}$		-16.32
		12.150		105.48
	411.527	2.430		115.43
		0.466		53.88
		0.097		27.03

88/146

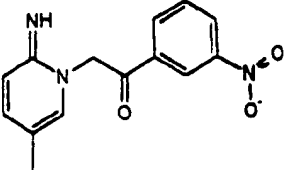
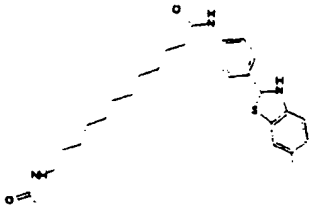
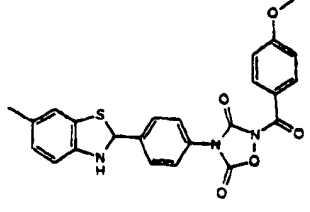
				
896-0686				
896-0686			191.774 $\mu$ M	-19.80
			19.177	176.04
260.724			3.835	115.02
			0.767	97.67
			0.153	25.27
				
896-0692				
896-0692			131.269 $\mu$ M	22.78
			13.127	149.23
360.897			2.625	78.33
			0.525	51.08
			0.105	46.12
				
896-0719				
896-0719			91.950 $\mu$ M	-6.49
			9.195	187.43
543.774			1.639	127.43
			0.369	50.04
			0.074	36.16
				
896-0773				
896-0773			147.228 $\mu$ M	-13.94
			14.723	175.33
339.609			2.945	221.91
			0.589	52.48
			0.118	32.98

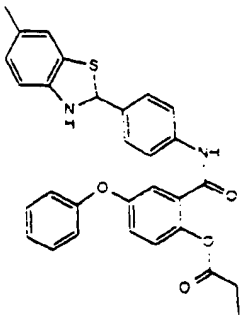
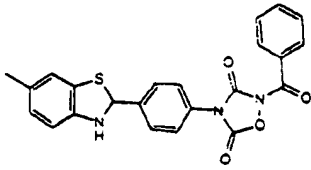
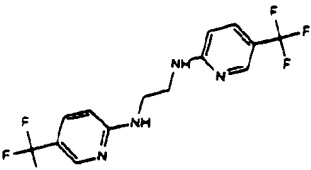
89/146

			
896-0819			
896-0819	124.219	uM	
	12.422		
402.516	2.484		
	0.497		
	0.089		
			
896-0853			
896-0853	157.548	uM	
	15.755		
317.357	3.151		
	0.630		
	0.128		
			
896-0821			
896-0821	174.583	uM	
	17.458		
286.397	3.492		
	0.688		
	0.140		

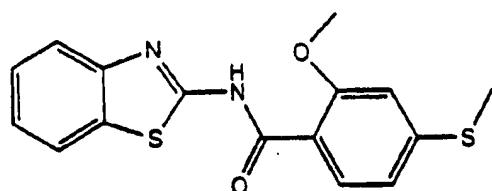
-16.20	
70.03	
165.79	
82.61	
49.06	
-27.08	
75.38	
208.69	
33.08	
32.63	
-19.59	
44.07	
103.23	
54.02	
23.86	

90/146

			
896-0836			
896-0836	184.314	uM	-16.20
	18.431		153.61
271.276	3.688		184.53
	0.737		79.16
	0.147		32.61
			
896-0859			
896-0859	103.798	uM	-1.73
	10.360		102.48
481.703	2.078		61.61
	0.415		63.58
	0.083		48.27
			
896-1201			
896-1201	108.343	uM	-45.70
	10.834		92.57
461.466	2.167		191.83
	0.433		47.22
	0.087		58.25

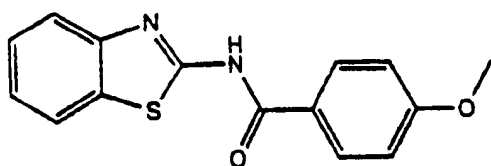
				
896-1301				
896-1301	97.922	uM		-24.32
	9.792			102.49
	510.612	1.958		139.28
		0.362		97.89
		0.078		23.45
				
896-1349				
896-1349	115.883	uM		-39.82
	11.588			55.05
	431.47	2.318		122.68
		0.484		67.25
		0.083		3.39
				
896-1362				
896-1362	142.749	uM		1,073.91
	14.275			1,082.17
	350.266	2.655		884.71
		0.571		-9.82
		0.114		-20.37

92/146



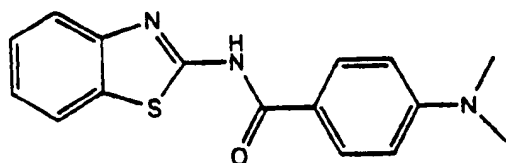
59-0072

Max : 215 %  
EC50 : < 0.8 nM



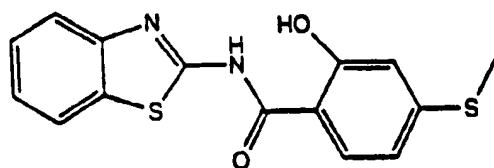
59-0102

Max : 121 %  
EC50 : 30 nM



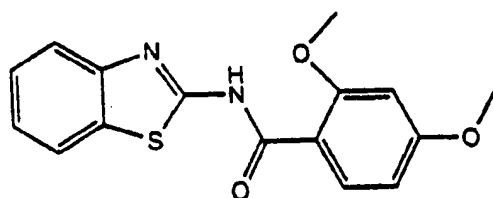
59-0070

Max : 214 %  
EC50 : 200 nM



59-0144

Max : 54 %  
EC50 : 2 μM

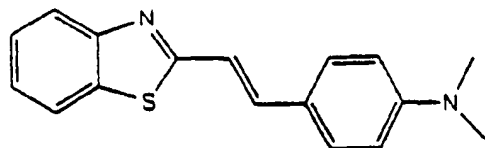


59-0147

Max : 340 %  
EC50 : < 0.8 nM

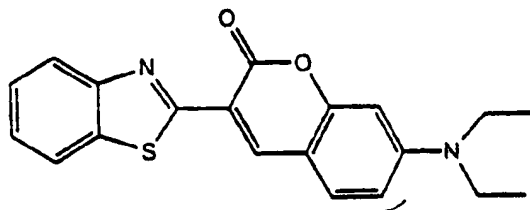
FIG. 5A

93 / 146

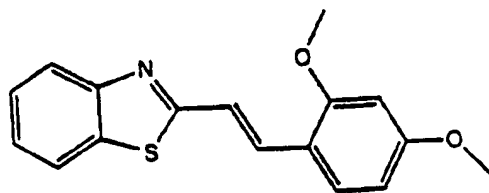


Max : 285 %  
EC50 : 3 nM

59-0099



Max : 269 %  
EC50 : < 0.8 nM



Max : 200 %  
EC50 : 30 nM

59-0210

5B  
FIG.

94/146

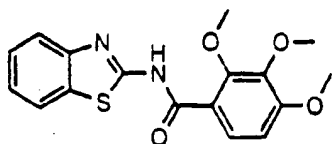
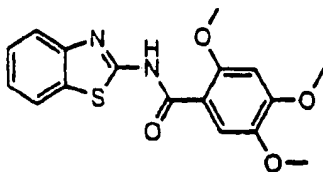
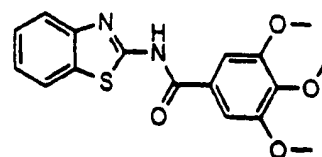
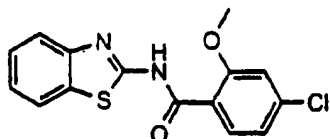
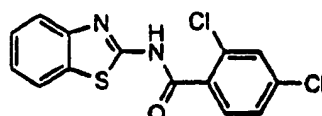
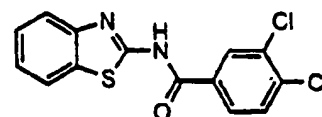
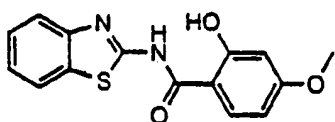
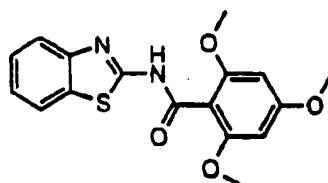
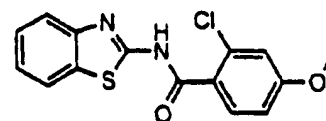
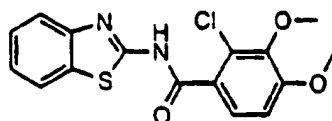
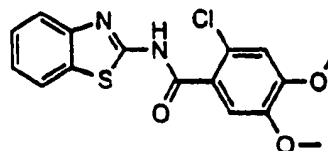
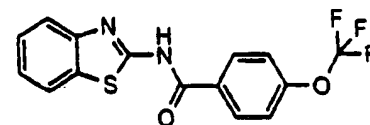
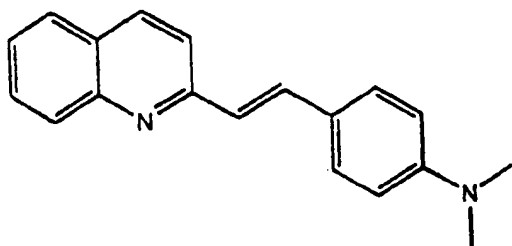
**59-0192****Max : 155 %****EC50 : 20 nM****59-0193****Max : 95 %****EC50 : 30 nM****59-0194****Inactive****59-0195****Max : 155 %****EC50 : 20 nM****59-0196****Inactive****59-0197****Max : 162 %****EC50 : 150 nM****59-0202****Max : 155 %****EC50 : 150 nM****59-0204****Max : 70 %****EC50 : 50 nM****59-0205****Max : 250 %****EC50 : < 0.8 nM****59-0206****Max : 150 %****EC50 : 20 nM****59-0207****Max : 50 %****EC50 : 100 nM****59-0208****Max : 85 %****EC50 : 1 uM**

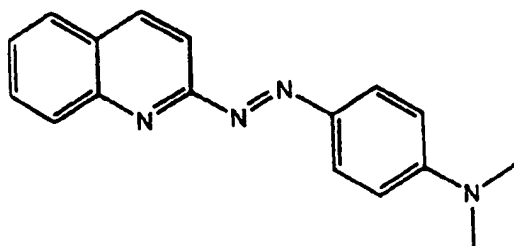
FIG.

5C





50-0197  
Max : 245 %  
EC50 : 3 nM



59-0078  
Max : 380 %  
EC50 : 1 nM

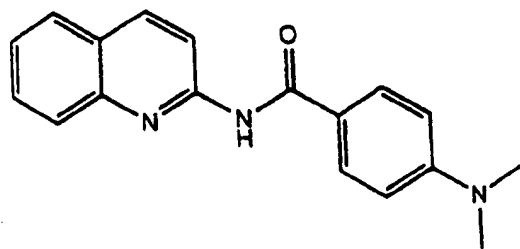
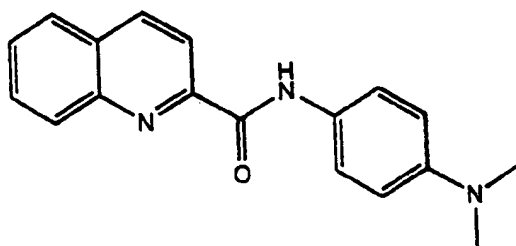
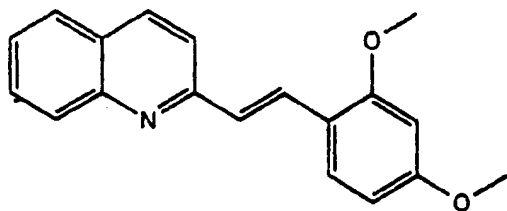
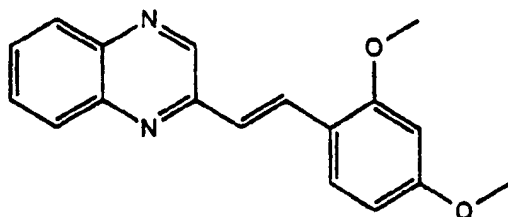


FIG. 6A

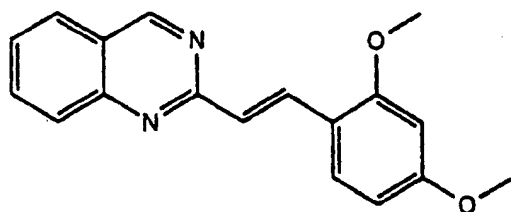
96/146



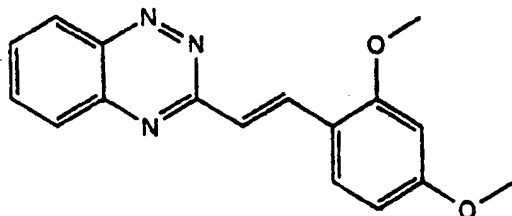
**59-0199**  
**Max : 170 %**  
**EC50 : 100 nM**



**59-0203**  
**Max : 275 %**  
**EC50 : < 1 nM**



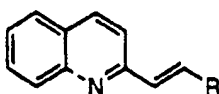
**59-0286**  
**Max : 160 %**  
**EC50 : 300 nM**



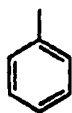
**59-0285**  
**Max : 200 %**  
**EC50 : 30 nM**

**FIG.** 6B

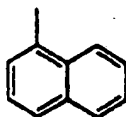
97/146



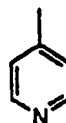
R =



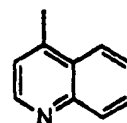
59-0030  
Max : 90 %  
EC50 : 1  $\mu$ M



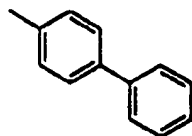
59-0089  
Max : 120 %  
EC50 : 5  $\mu$ M



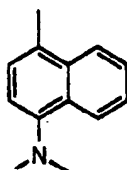
59-0093  
Max : 35 %



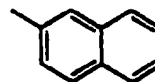
59-0094  
Max : 45 %



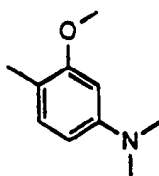
59-0091  
Max : 96 %  
EC50 : 1  $\mu$ M



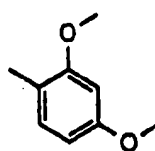
59-0090  
Max : 41 %



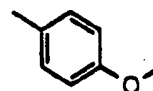
59-0092  
Max : 50 %  
EC50 : 10  $\mu$ M



59-0150  
Max : 500 %  
EC50 : 1 nM



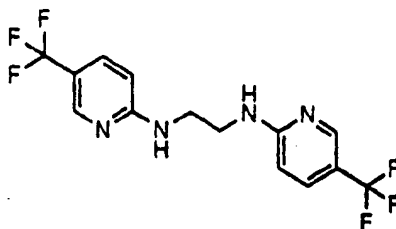
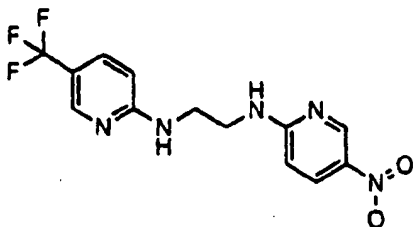
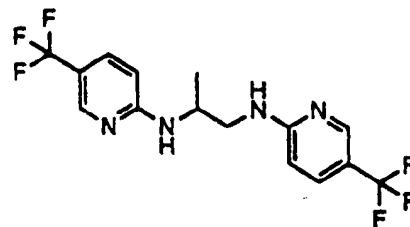
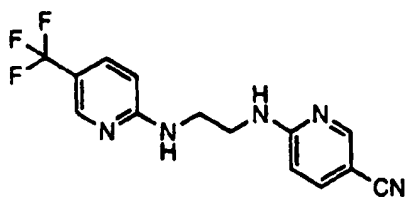
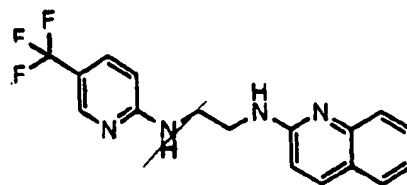
59-0199  
Max : 170 %  
EC50 : 100 nM

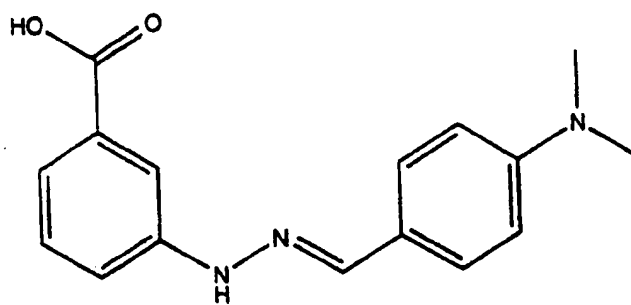


59-0198  
Max : 135 %  
EC50 : 100 nM

FIG. <sup>6C</sup>

98 / 146

**59-0145****Max : 300 %  
EC50 : 0.5 uM****59-0450****Max : 270 %  
EC50 : 5 uM****59-0459****Max : 180 %  
EC50 : 5 uM****59-0483****Max : 260 %  
EC50 : 3 uM****59-0480****Max : 180 %  
EC50 : 5 uM**7  
**FIG.**

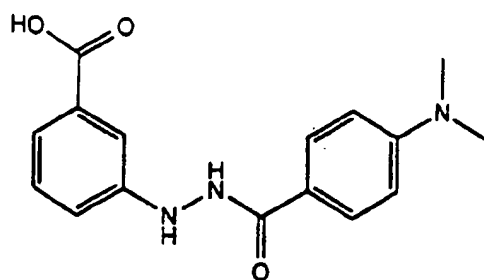


59-0045

EC<sub>50</sub> = 5 nM

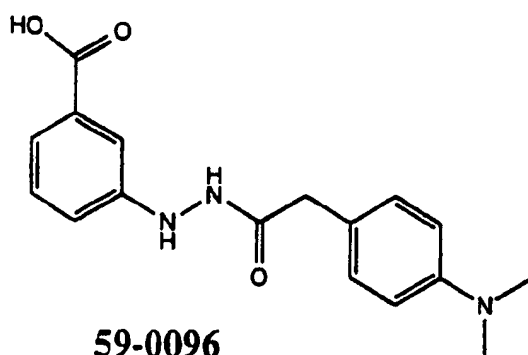
FIG. 8A

100 / 146



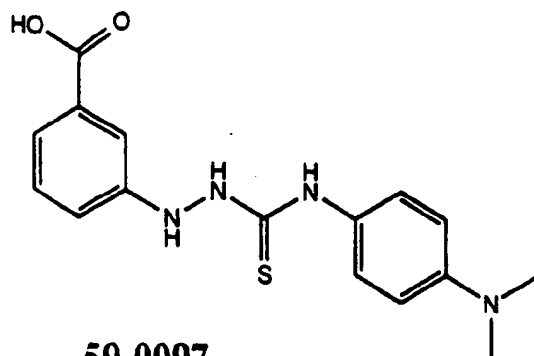
59-0095

Max : 48 %  
EC50 : 30  $\mu$ M



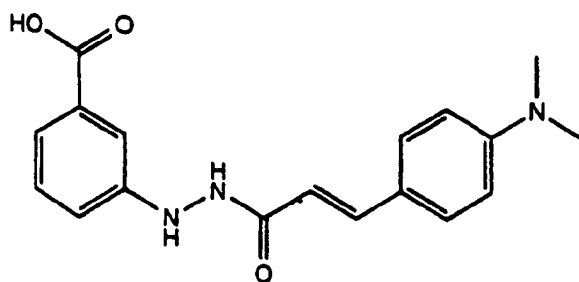
59-0096

Max : 413 %  
EC50 : 93 nM



59-0097

Max : 202 %  
EC50 : 100 nM



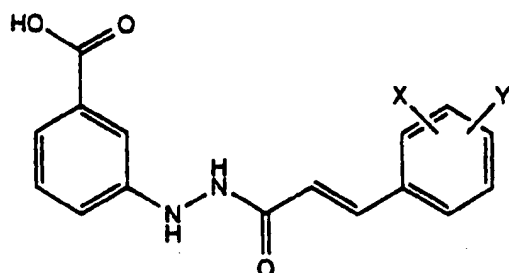
59-0098

Max : 222 %  
EC50 : 20 nM

FIG.

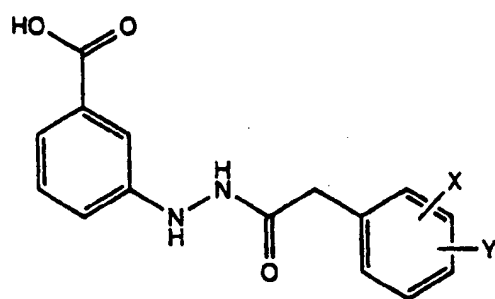
86

101 / 146



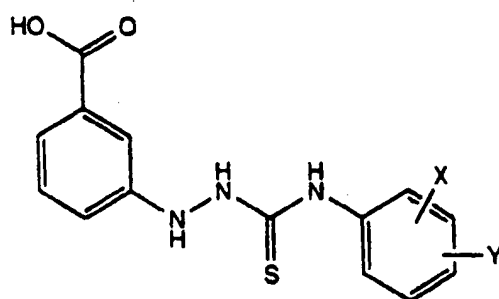
X, Y = F, Cl, OMe

&lt; 50 % max @ 100 uM

**59-0098 Analogs**

X, Y = F, Cl, OMe

&lt; 50 % max @ 100 uM

**59-0096 Analogs**

X, Y = F, Cl, OMe

&lt; 50 % max @ 100 uM

**59-0097 Analogs**8c  
**FIG.**

102 / 146

Score

Compound	Compound	EC50	Max	ZGI Score in	
	Class		Response of 59-0008	Ex Vivo Assay	OS Screen in Ex Vivo Assay
59-0364	P	0	0	1	
59-0076	P	0	0	1	
59-0451	P	0	0	1	
59-0472	P	0	0	1	
59-0073	P	0	0		1+
59-0095	H	??	0.5x (30 uM)		1
59-0471	P	??	0.5x (100 uM)	1	
59-0030	Q	??	.7x (1 uM)	1	1,1+
59-0470	P	50 uM	1.2x (100 uM)	1	
59-0450	P	5 uM	2.7x (30 uM)		
59-0459	P	5 uM	2x (10 uM)	1	
59-0064	Q	3 uM	1.5x (? uM)	1	

59-0008	Q	1 uM			1
59-0125	H	300 nM	2x (3 uM)	1-2	1-2
59-0106	T	300 nM	2x (9 uM)		1
59-0070	T	200nM	2x (3 uM)		1,1+
59-0097	H	100 nM?	2x (30 uM)		1+
59-0096	H	100 nM?	4x (100 uM)		1
59-0116	H	30 nM	2.5x (3 uM)		1+,2-
59-0210	T	30 nM	2x (3 uM)		1
59-0098	H	20 nM	2x (3 uM)	1-2	1-2
59-0019	Q	10 nM	2.5x (300 nM)	1+,2-	1,1+
59-0078	Q	9 nM	4x (1 uM)		1
59-0045	H	5 nM	4x (1 uM)	1	1
50-0197	Q	3 nM	2.5x (300 nM)	1	1+,2-
59-0099	T	2 nM?	3x (1 uM)		1,1+
59-0282	Q	1 nM	2x (3 uM)		1+,2-
59-0203	Q	1 nM	2x (3 uM)		2,3
59-0072	T	300 pM	2x (uM)	1-1+	1,1+
59-0150	Q	<1 nM	5x (3 uM)	1-2?	1
59-0104	T	<1 nM	2x (uM)	1+,2-	1
59-0103	T	<1 nM	2x (30 nM)		1,1+
59-0124	T	<1 nM	2.5x (1 uM)		1+,2-
59-0205	T	<1 nM	2x (2 nM)		1

H = Hydrazone/Hydrazide (45)    T = Benzothiazole (104)  
 Q = Quinoline/Quinoxaline (197)  
 P = Bis-pyridines (145)

Figur 9



103/146

Tx-3A: Lumbar vertebra  
% Cancellous bone vol

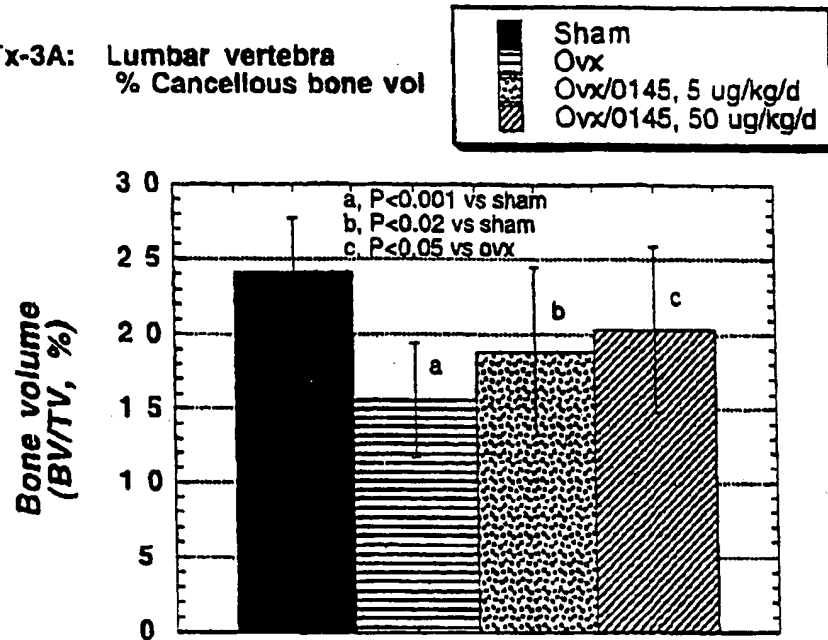
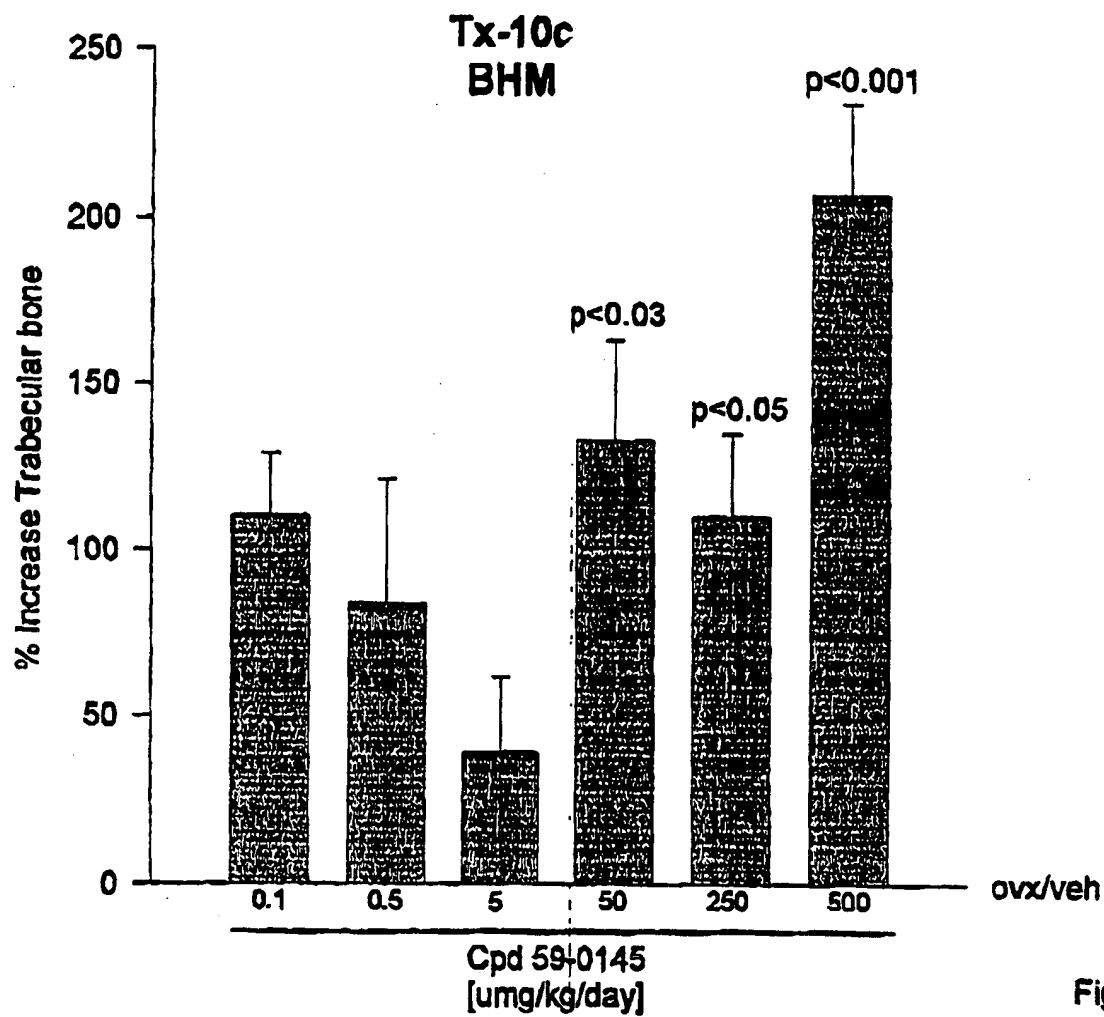


Fig 10

104 / 146



% Increase of trabecular bone over the ovx/vehicle group

Fig  
11

105 / 146

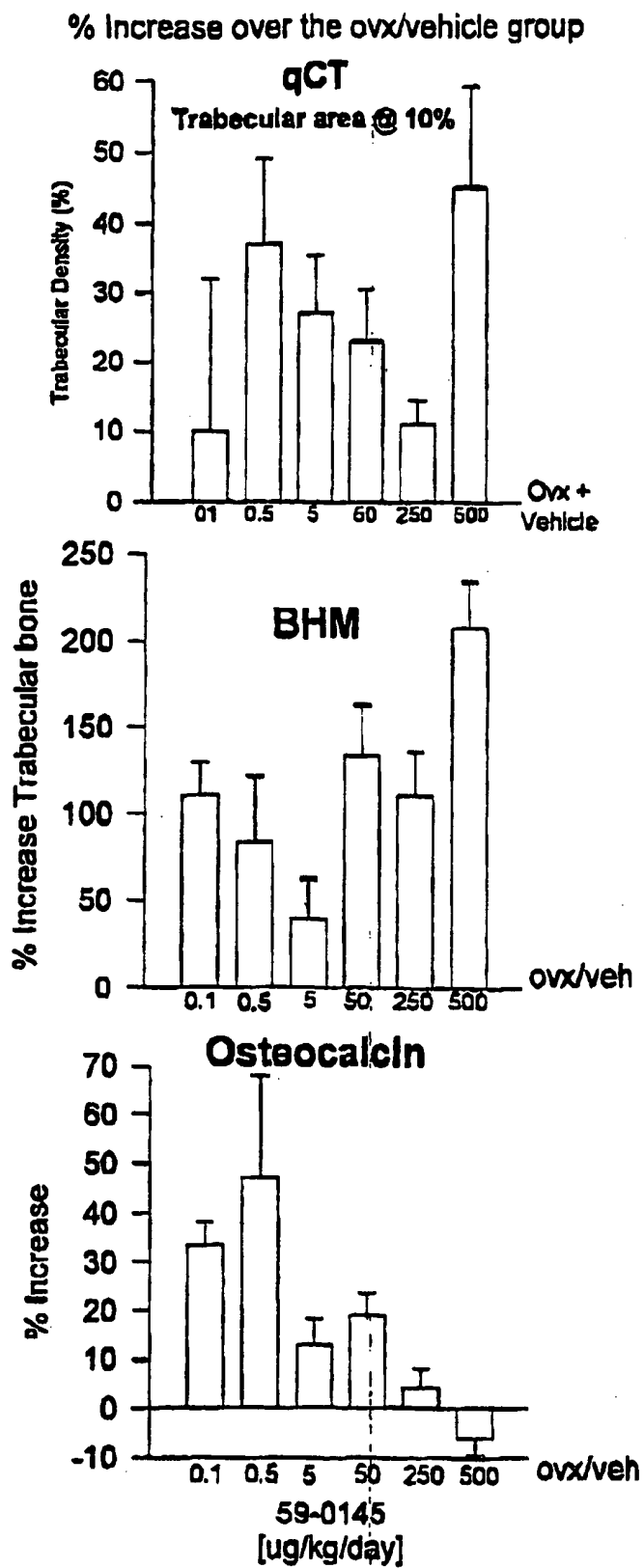
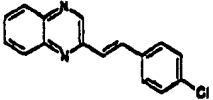
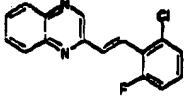
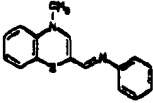
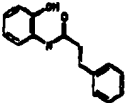
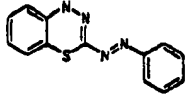
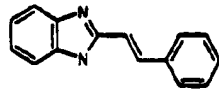
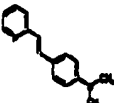
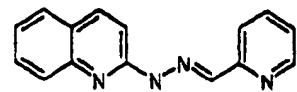
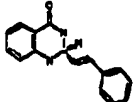
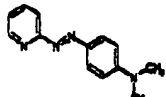
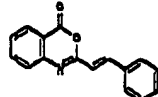
**Tx-10c**

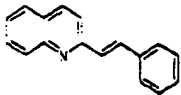
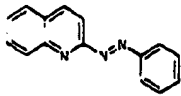
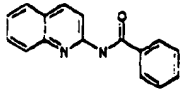
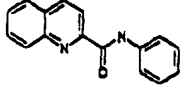
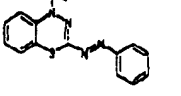
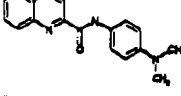
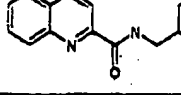
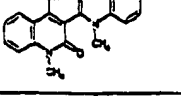
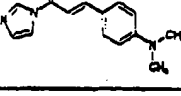
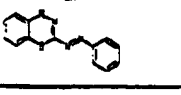
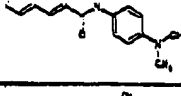
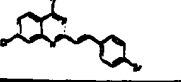
Fig 12

nand2

MOLSTRUCTURE	MOL>NNC	MOL WEIGHT	NUM1
	59-0020	266.732	
	59-0021	284.723	
	59-0022	266.367	
	59-0023	239.276	
	59-0008	254.315	
	59-0024	220.276	
	59-0025	224.308	
	59-0026	248.29	
	59-0027	250.303	
	59-0028	226.283	
	59-0029	249.272	

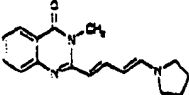
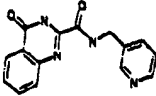
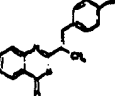
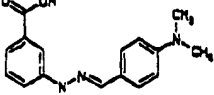
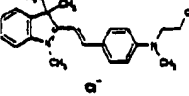
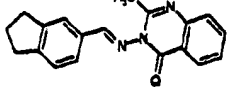
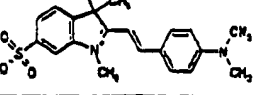
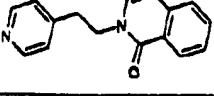

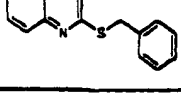
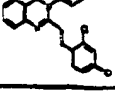

107/146

nand2

	59-0031	231.3	
	59-0030	233.275	
	59-0032	248.287	
	59-0033	248.287	
	59-0034	268.343	
	59-0035	291.356	
	59-0036	262.314	
	59-0037	308	
	59-0038	241.295	
	59-0039	312.352	
	59-0040	290.368	
	59-0041	501.902	

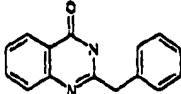
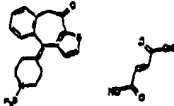
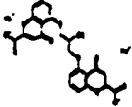
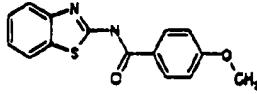
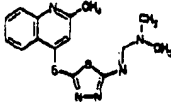
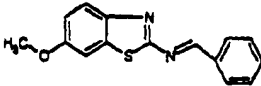
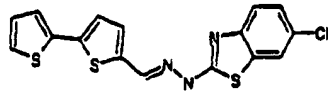
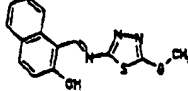
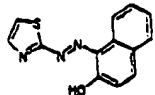
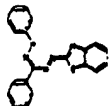
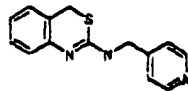
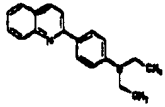
108 / 146

nand2

	59-0042	281.361
	59-0043	280.288
	59-0044	341.21
	59-0045	283.333
	59-0046	389.372
	59-0047	303.367
	59-0048	384.501
	59-0049	251.29
	59-0050	303.364
	59-0051	251.353
	59-0052	393.276
	59-0053	354.412

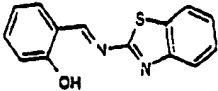
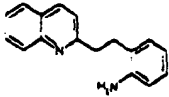
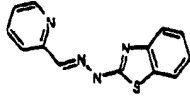
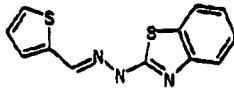
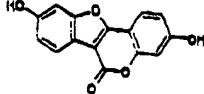
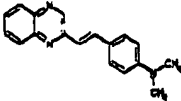
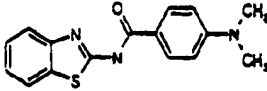
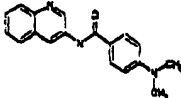
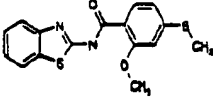
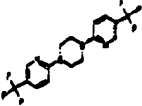
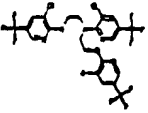
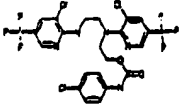
109 / 146

nand2

	59-0054	236.276	
	59-0055	425.508	
	59-0056	512.341	
	59-0102	284.339	
	59-0057	329.448	
	59-0058	268.34	
	59-0059	375.923	
	59-0060	301.391	
	59-0061	255.3	
	59-0062	357.44	
	59-0063	255.344	
	59-0064	276.385	

110 / 146

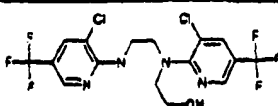
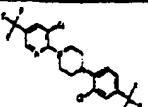
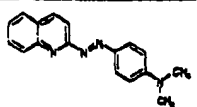
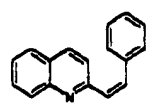
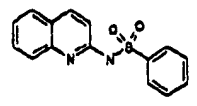
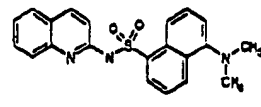
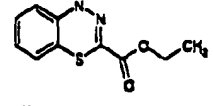
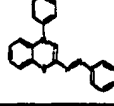
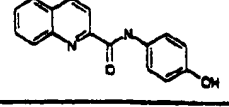
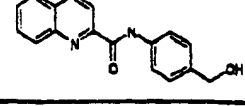
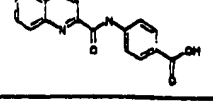
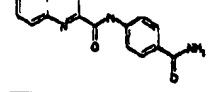
nand2

	59-0065	254.313	
	59-0066	248.33	
	59-0067	254.315	
	59-0068	259.354	
	59-0069	268.223	
	59-0019	275.353	
	59-0070	297.38	
	59-0071	291.352	
	59-0072	330.431	
	59-0073	376.303	
	59-0074	642.735	
	59-0075	618.775	



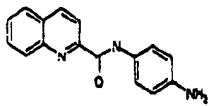
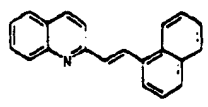
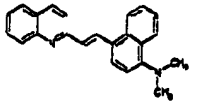
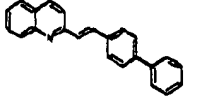
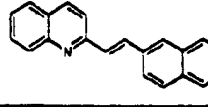
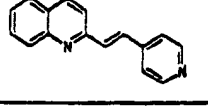
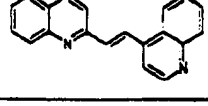
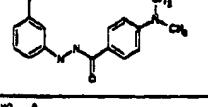
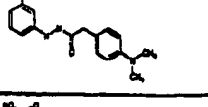
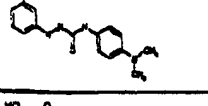
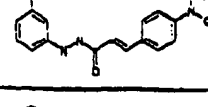
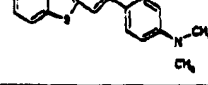
111 / 146

nand2

	59-0076	463.208	
	59-0077	445.193	
	59-0078	276.341	
	59-0079	231.297	
	59-0080	284.338	
	59-0081	377.466	
	59-0082	222.267	
	59-0083	330.414	
	59-0084	264.283	
	59-0085	278.31	
	59-0086	292.293	
	59-0087	291.309	

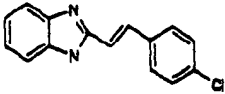
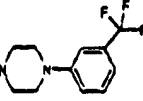
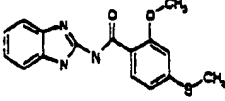
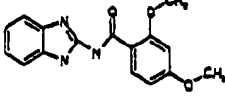
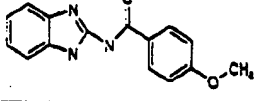
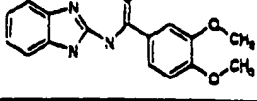
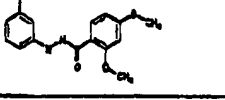
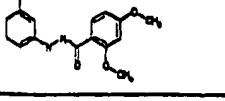
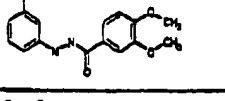
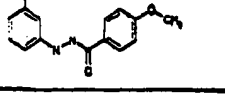
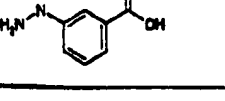
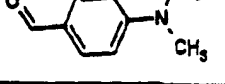
112/146

nand2

	59-0088	263.299	
	59-0089	281.357	
	59-0090	324.425	
	59-0091	307.394	
	59-0092	281.357	
	59-0093	232.285	
	59-0094	282.345	
	59-0095	299.328	
	59-0096	313.355	
	59-0097	330.41	
	59-0098	325.368	
	59-0099	280.393	

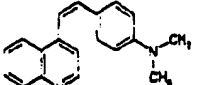
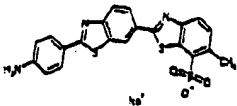
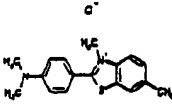
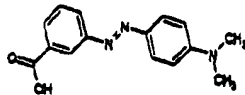
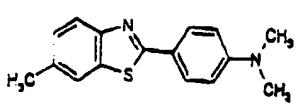
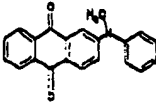
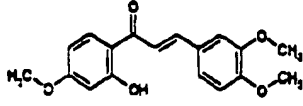
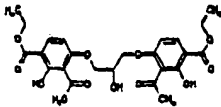
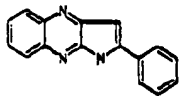
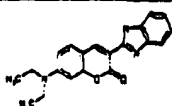
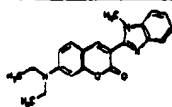
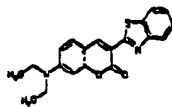
113 / 146

nand2

	59-0100	254.719	
	59-0101	230.232	
	59-0103	313.379	
	59-0104	297.312	
	59-0105	267.287	
	59-0106	297.312	
	59-0107	332.378	
	59-0108	316.311	
	59-0109	316.311	
	59-0110	286.286	
	59-0111	152.152	
	59-0112	149.192	

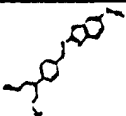
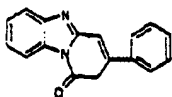
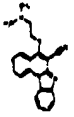
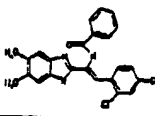
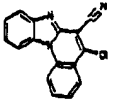
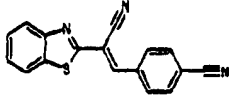
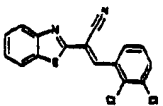
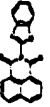
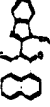
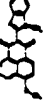
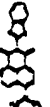
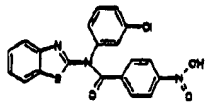
114/146

nand2

	59-0113	274.365	
	59-0114	475.548	
	59-0115	318.87	
	59-0116	269.302	
	59-0117	268.382	
	59-0118	313.354	
	59-0119	314.335	
	59-0120	504.485	
	59-0121	245.284	
	59-0122	333.389	
	59-0123	347.416	
	59-0124	350.44	

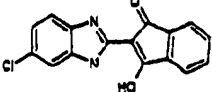
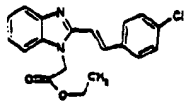
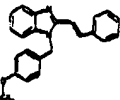
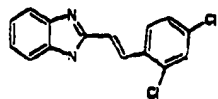
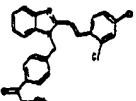
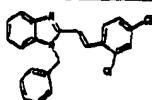
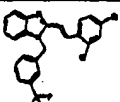
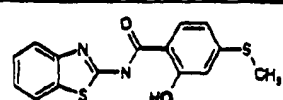
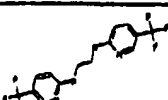
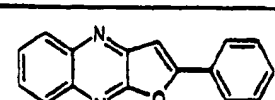
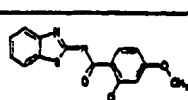
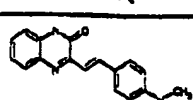
115 / 146

nand2

	59-0125	372.447	
	59-0126	260.295	
	59-0127	329.405	
	59-0128	436.34	
	59-0129	277.713	
	59-0130	287.345	
	59-0131	331.225	
	59-0132	313.315	
	59-0133	327.342	
	59-0134	357.367	
	59-0135	356.383	
	59-0136	411.868	

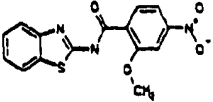
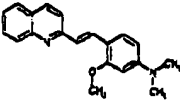
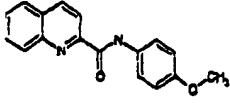
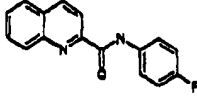
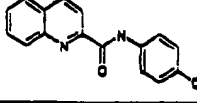
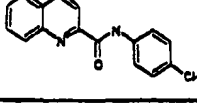
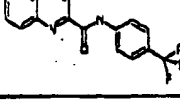
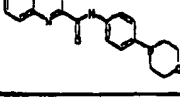
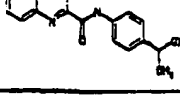
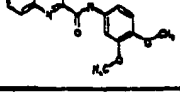
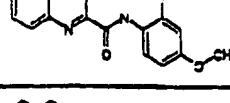
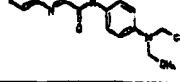
116 / 146

nand2

	59-0137	296.712	
	59-0138	340.808	
	59-0139	340.424	
	59-0140	289.164	
	59-0141	437.324	
	59-0142	379.288	
	59-0143	447.285	
	59-0144	316.404	
	59-0145	350.265	
	59-0146	246.268	
	59-0147	314.364	
	59-0148	291.352	

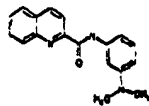
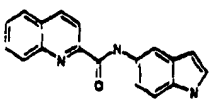
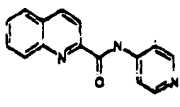
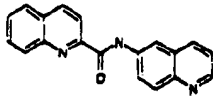
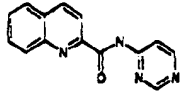
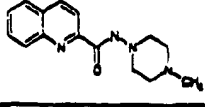
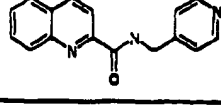
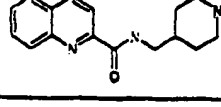
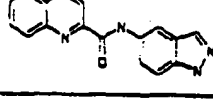
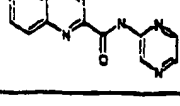
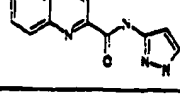
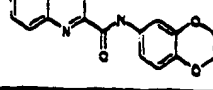
117/146

nand2

	59-0149	329.335	
	59-0150	304.391	
	59-0151	278.31	
	59-0152	266.274	
	59-0153	282.729	
	59-0154	262.311	
	59-0155	316.281	
	59-0156	333.389	
	59-0157	290.364	
	59-0158	308.335	
	59-0159	308.335	
	59-0160	319.406	

118/146

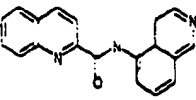
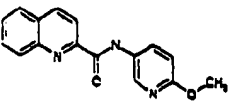
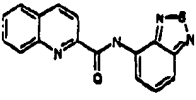
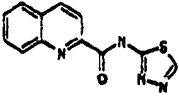
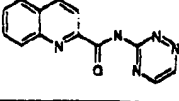
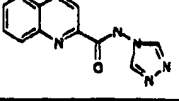
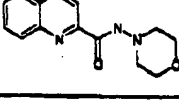
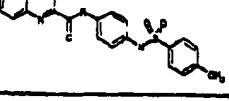
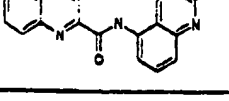
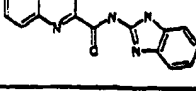
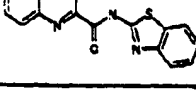
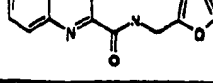
nand2

	59-0161	291.352	
	59-0162	287.321	
	59-0163	249.272	
	59-0164	299.332	
	59-0165	250.26	
	59-0166	270.334	
	59-0167	263.298	
	59-0168	269.346	
	59-0169	288.309	
	59-0170	250.26	
	59-0171	238.249	
	59-0172	306.32	



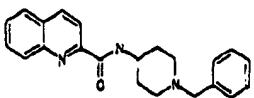
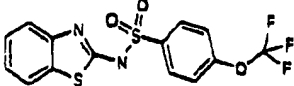
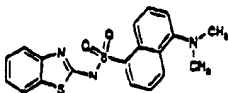
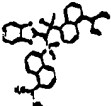
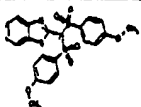
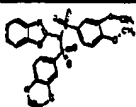
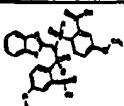
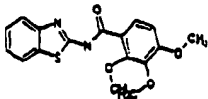
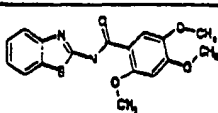
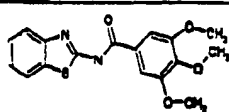
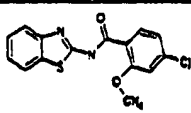
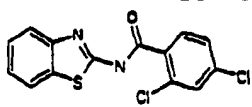
119 / 146

nand2

	59-0173	299.332	
	59-0174	279.298	
	59-0175	306.348	
	59-0176	256.288	
	59-0177	251.248	
	59-0178	239.287	
	59-0179	257.292	
	59-0180	417.487	
	59-0181	313.358	
	59-0182	288.309	
	59-0183	305.36	
	59-0184	252.272	

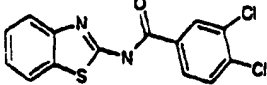
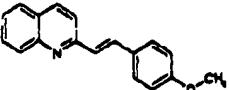
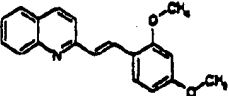
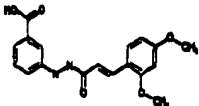
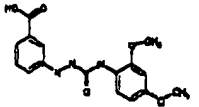
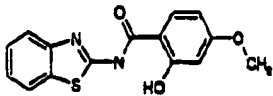
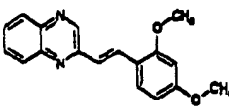
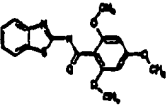
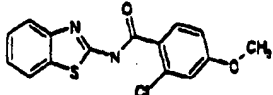
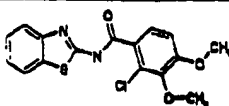
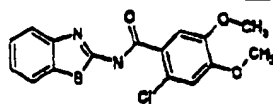
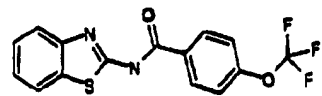
120/146

nand2

	59-0185	345.444	
	59-0186	374.362	
	59-0187	389.494	
	59-0188	616.784	
	59-0189	490.579	
	59-0190	550.631	
	59-0191	584.605	
	59-0192	344.389	
	59-0193	344.389	
	59-0194	344.389	
	59-0195	318.783	
	59-0196	323.202	

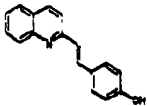
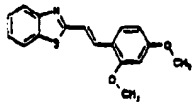
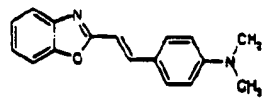
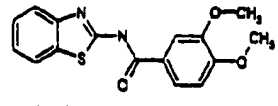
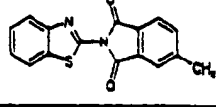
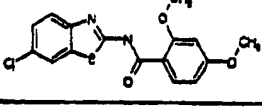
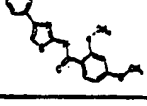
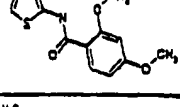
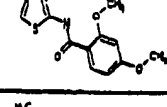
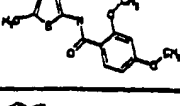
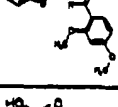
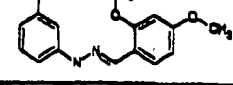
121 / 146

nand2

	59-0197	323.202	
	59-0198	261.323	
	59-0199	291.348	
	59-0200	342.349	
	59-0201	331.326	
	59-0202	300.337	
	59-0203	292.336	
	59-0204	344.389	
	59-0205	318.783	
	59-0206	348.809	
	59-0207	348.809	
	59-0208	338.308	

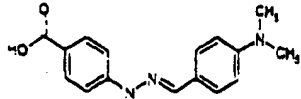
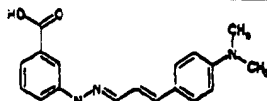
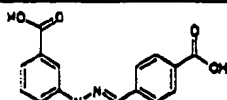
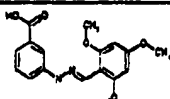
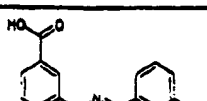

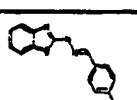
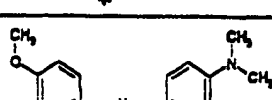
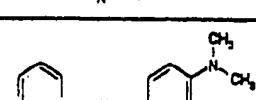
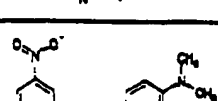


122 / 146

nand2

	59-0209	247.296	
	59-0210	297.376	
	59-0211	264.326	
	59-0212	314.364	
	59-0213	294.333	
	59-0214	348.809	
	59-0215	340.401	
	59-0216	264.304	
	59-0217	278.331	
	59-0218	292.357	
	59-0219	329.379	
	59-0220	300.312	

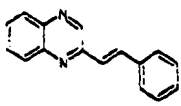
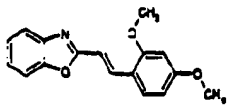
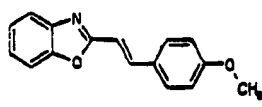
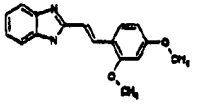
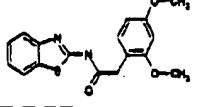
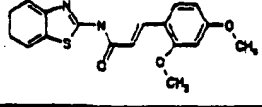
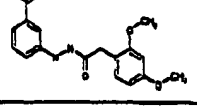
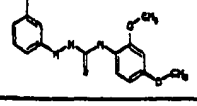
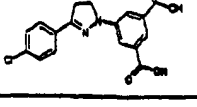
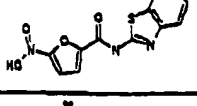
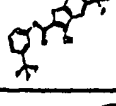
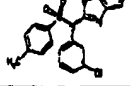
123 / 146

nand2

	59-0221	283.329	
	59-0222	309.367	
	59-0223	284.27	
	59-0224	330.338	
	59-0225	256.26	
	59-0226	285.258	
	59-0227	296.398	
	59-0228	269.346	
	59-0229	239.32	
	59-0230	284.317	
	59-0231	318.399	
	59-0232	269.35	

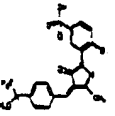
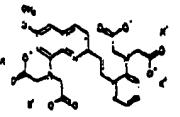
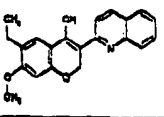
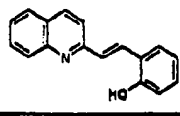
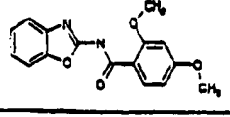
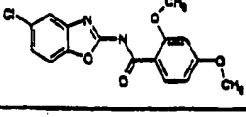
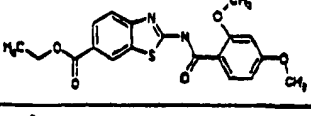
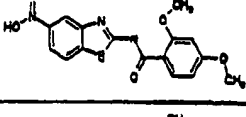
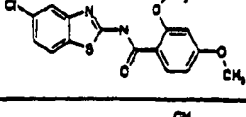
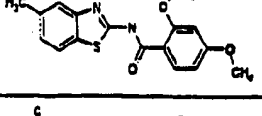
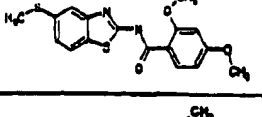
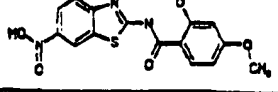
124 / 146

nand2

	59-0233	232.285	
	59-0234	281.31	
	59-0235	251.284	
	59-0236	280.325	
	59-0237	328.39	
	59-0238	340.401	
	59-0239	330.338	
	59-0240	347.393	
	59-0241	344.753	
	59-0242	291.286	
	59-0243	455.934	
	59-0244	414.935	

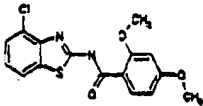
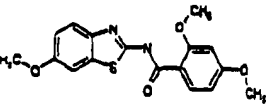
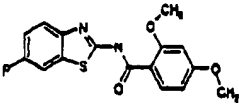
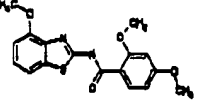
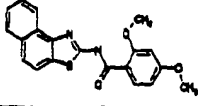
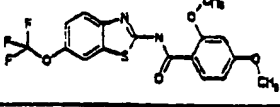
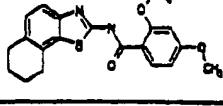
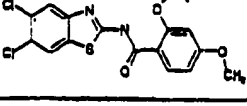
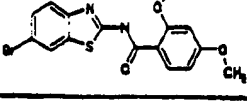
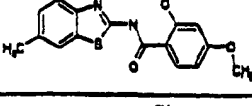
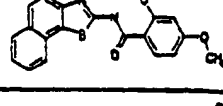
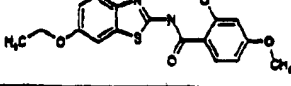
125 / 146

nand2

	59-0245	419.887	
	59-0246	675.856	
	59-0247	933.385	
	59-0248	247.296	
	59-0249	298.297	
	59-0250	332.742	
	59-0251	386.426	
	59-0252	361.376	
	59-0253	348.809	
	59-0254	328.39	
	59-0255	376.455	
	59-0256	381.376	

126 / 146

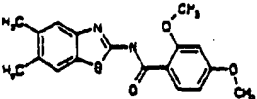
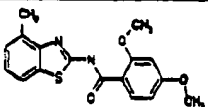
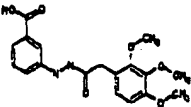
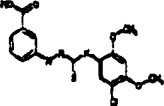
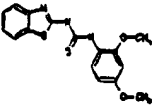
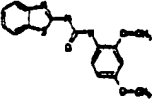
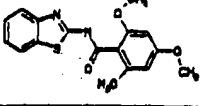
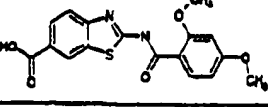
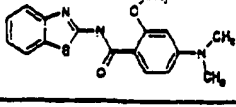
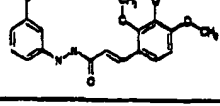
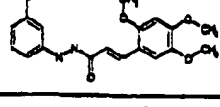
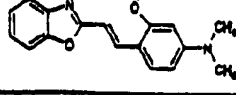
nand2

	59-0257	348.809	
	59-0258	344.389	
	59-0259	332.354	
	59-0260	344.389	
	59-0261	354.423	
	59-0262	398.36	
	59-0263	368.455	
	59-0264	383.254	
	59-0265	393.26	
	59-0266	328.39	
	59-0267	364.423	
	59-0268	358.416	



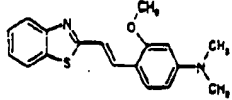
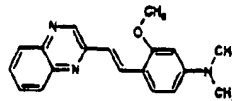
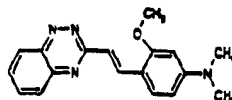
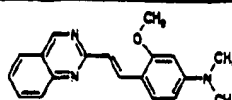
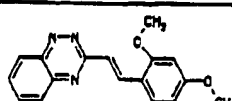
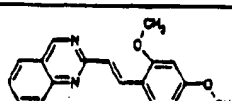
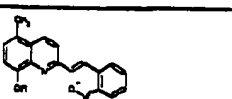
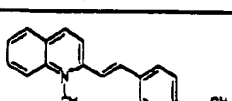
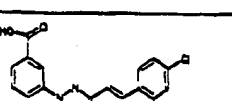
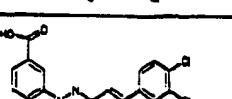
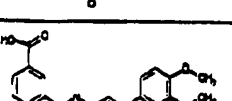
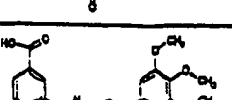
127 / 146

nand2

	59-0269	342.417	
	59-0270	328.39	
	59-0271	360.364	
	59-0272	361.838	
	59-0273	345.445	
	59-0274	329.379	
	59-0275	328.39	
	59-0276	358.373	
	59-0279	327.406	
	59-0277	372.375	
	59-0278	372.375	
	59-0280	294.352	

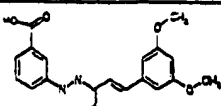
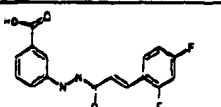
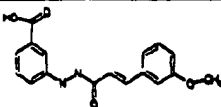
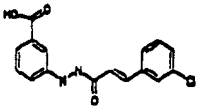
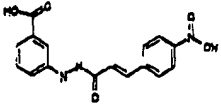
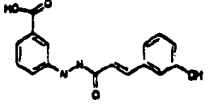
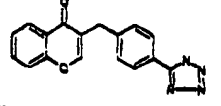
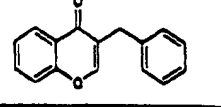
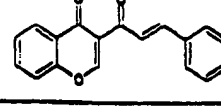
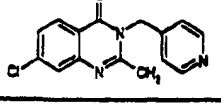
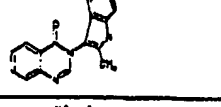
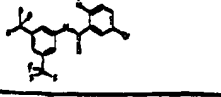
128/146

nand2

	59-0281	310.419	
	59-0282	305.379	
	59-0283	306.367	
	59-0284	305.379	
	59-0285	293.324	
	59-0286	282.336	
	59-0287	306.32	
	59-0288	276.357	
	59-0289	351.188	
	59-0290	351.188	
	59-0291	342.949	
	59-0292	372.375	

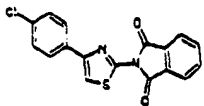
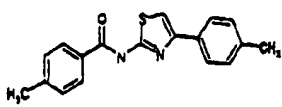
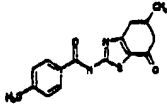
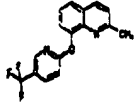
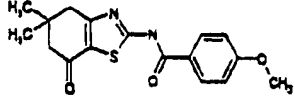
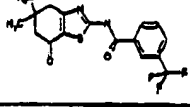
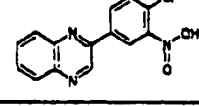
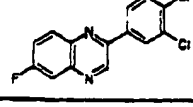
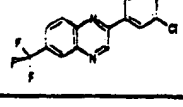
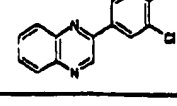
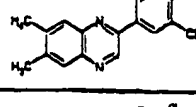
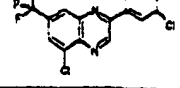
129/146

nand2

	59-0293	342.349	
	59-0294	318.278	
	59-0295	312.323	
	59-0296	318.743	
	59-0297	329.31	
	59-0298	298.297	
	59-0299	304.308	
	59-0300	236.269	
	59-0301	326.35	
	59-0302	285.733	
	59-0303	275.31	
	59-0304	469.178	

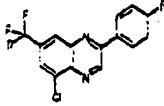
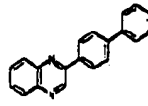
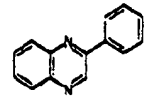
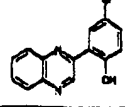
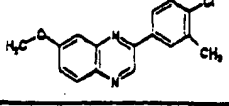
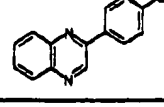
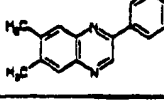
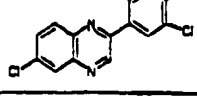
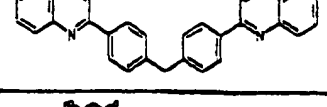
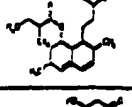
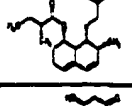
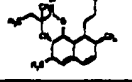
130/146

nand2

	59-0305	340.789	
	59-0306	308.403	
	59-0307	300.38	
	59-0308	304.27	
	59-0309	330.406	
	59-0310	368.378	
	59-0311	287.705	
	59-0313	293.127	
	59-0314	343.134	
	59-0315	275.137	
	59-0316	303.191	
	59-0317	377.579	

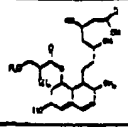
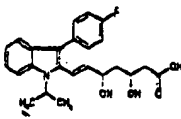
131 / 146

nand2

	59-0318	326.6791	
	59-0319	282.345	
	59-0320	208.247	
	59-0321	256.691	
	59-0322	284.745	
	59-0323	285.143	
	59-0324	294.301	
	59-0312	309.582	
	59-0325	424.505	
	59-0326	404.543	
	59-0327	390.517	
	59-0328	418.57	

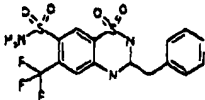
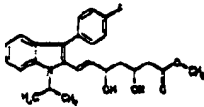
132 / 146

nand2

	59-0329	424.53	
	59-0330	411.47	

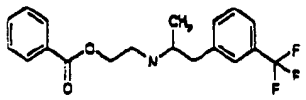
133 / 146

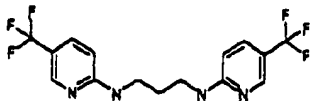
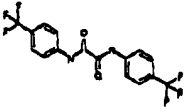
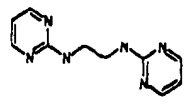
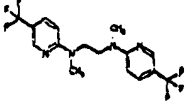
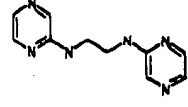
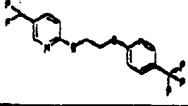
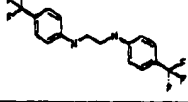
nand2

	59-0354	421.419
	59-0342	425.497

134/146

nand2

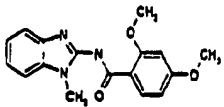
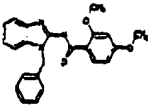
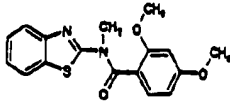
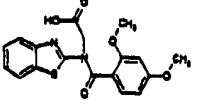
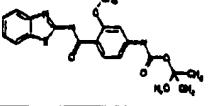
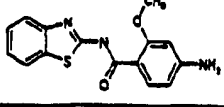
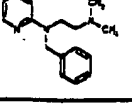
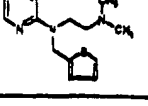
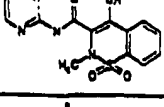
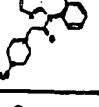
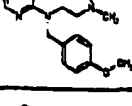
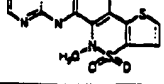
	59-0357	351.368	
---	---------	---------	--

	59-0361	364.292	
	59-0362	376.255	
	59-0363	216.247	
	59-0364	378.318	
	59-0365	216.247	
	59-0366	384.367	
	59-0367	348.289	



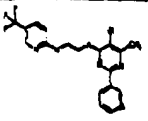
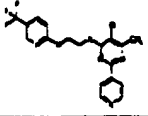
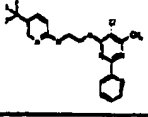
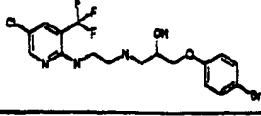
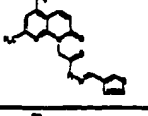
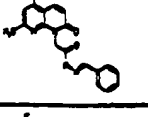
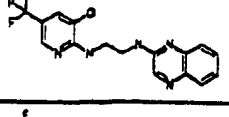
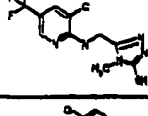
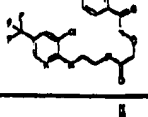
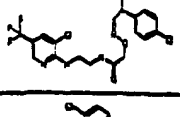
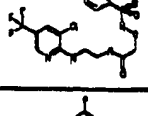
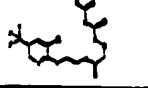
135/146

nand2

	59-0368	311.339	
	59-0369	387.437	
	59-0370	328.39	
	59-0371	372.399	
	59-0372	399.469	
	59-0373	299.353	
	59-0374	255.363	
	59-0375	261.391	
	59-0376	331.351	
	59-0377	351.408	
	59-0378	285.389	
	59-0379	337.379	

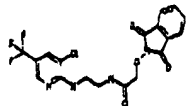
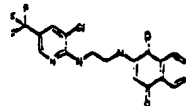
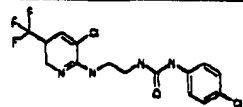
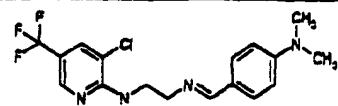
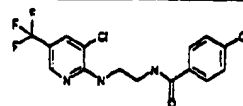
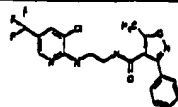
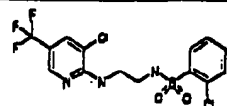
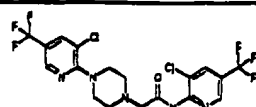
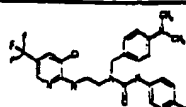
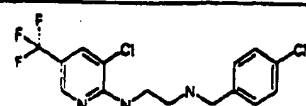
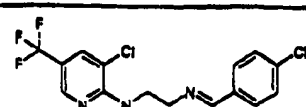
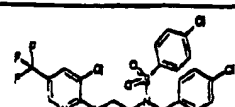
136 / 146

nand2

	59-0380	408.813	
	59-0381	408.813	
	59-0382	408.813	
	59-0383	488.699	
	59-0384	340.405	
	59-0385	334.377	
	59-0386	367.761	
	59-0387	923.729	
	59-0388	451.23	
	59-0389	474.268	
	59-0390	487.284	
	59-0391	466.245	

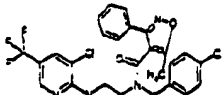
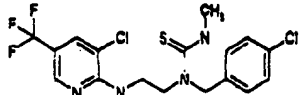
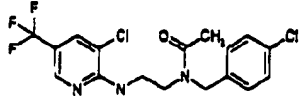
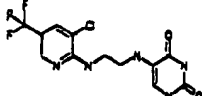
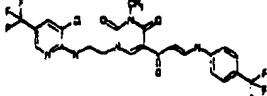
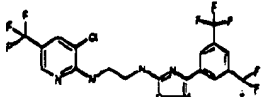
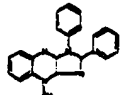
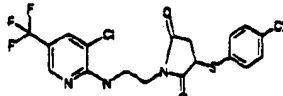
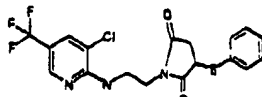
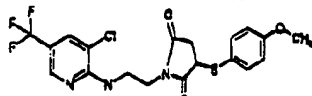
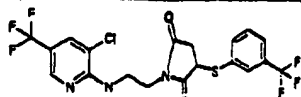
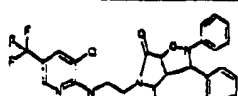
137 / 146

nand2

	59-0392	442.78	
	59-0393	395.767	
	59-0394	393.195	
	59-0395	370.804	
	59-0396	378.18	
	59-0397	424.808	
	59-0398	414.234	
	59-0399	502.245	
	59-0400	526.388	
	59-0401	364.187	
	59-0402	382.181	
	59-0403	538.803	

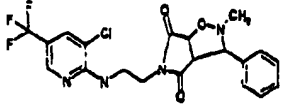
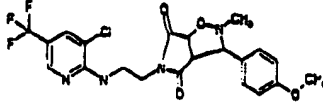
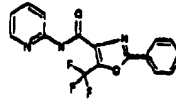
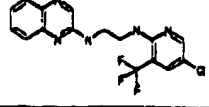
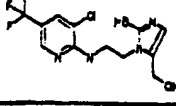
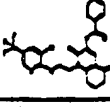
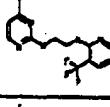
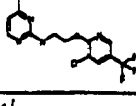
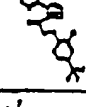
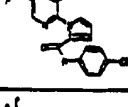
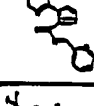

138 / 146

nand2

	59-0404	549.378
	59-0405	437.315
	59-0406	406.233
	59-0407	349.699
	59-0408	561.868
	59-0409	535.821
	59-0410	340.428
	59-0411	464.294
	59-0412	429.849
	59-0413	459.874
	59-0414	497.846
	59-0415	516.905

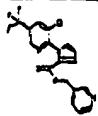
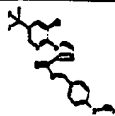
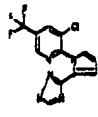
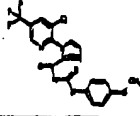
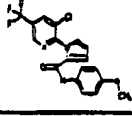
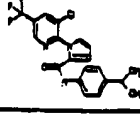
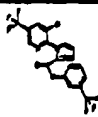
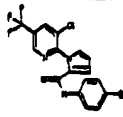
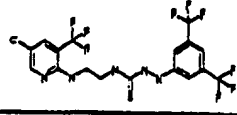
139 / 146

nand2

	59-0416	454.834	
	59-0417	484.86	
	59-0418	333.268	
	59-0419	367.761	
	59-0420	352.787	
	59-0421	539.339	
	59-0422	351.259	
	59-0423	385.698	
	59-0424	484.188	
	59-0425	400.186	
	59-0426	380.756	
	59-0427	414.213	

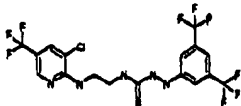
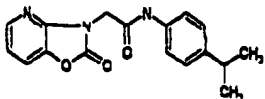
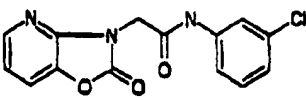
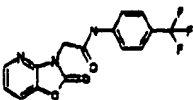
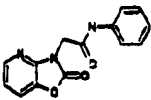


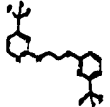
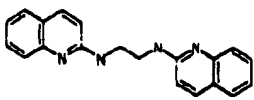
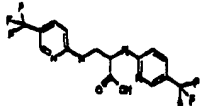
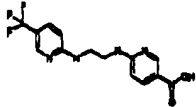
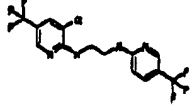
140/146

nand2

	59-0428	380.756	
	59-0429	409.793	
	59-0430	313.669	
	59-0431	454.859	
	59-0432	395.767	
	59-0433	407.821	
	59-0435	433.738	
	59-0436	444.637	
	59-0439	525.826	

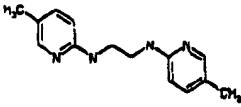
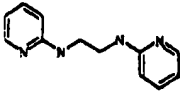
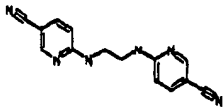
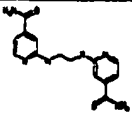
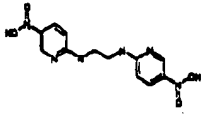
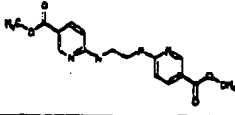
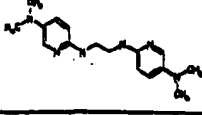
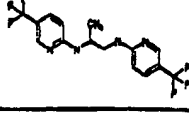
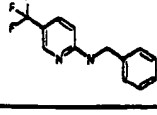
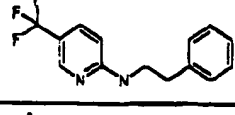
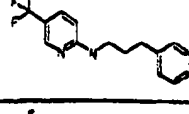
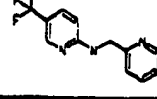
141 / 146

nand2

	59-0440	525.826	
	59-0441	311.339	
	59-0442	303.704	
	59-0443	337.256	
	59-0444	269.259	
	59-0445	404.356	
	59-0446	404.356	
	59-0447	352.241	
	59-0448	314.39	
	59-0449	394.274	
	59-0450	329.281	
	59-0451	384.71	

142 / 146

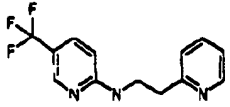
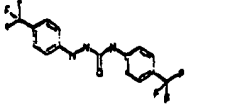
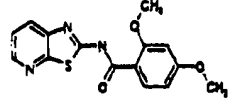
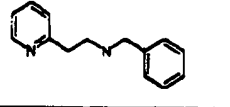
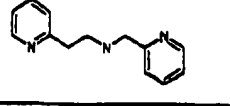
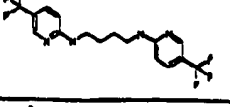
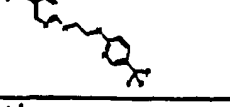
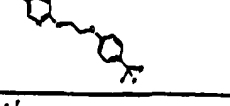
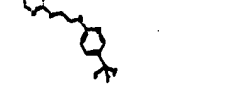
nand2

	59-0452	242.324
	59-0453	214.271
	59-0454	264.291
	59-0455	300.32
	59-0456	308.296
	59-0457	330.342
	59-0458	300.408
	59-0459	364.292
	59-0460	252.238
	59-0461	266.265
	59-0462	280.292
	59-0463	253.226



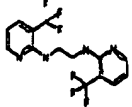
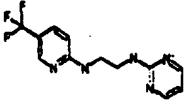
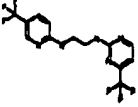
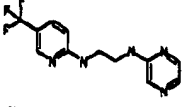
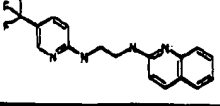
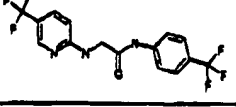
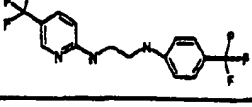
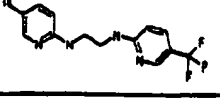
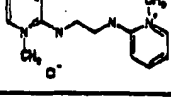
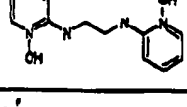
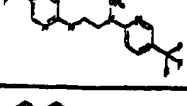
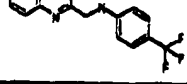
143 / 146

nand2

	59-0464	267.253	
	59-0465	363.26	
	59-0466	316.352	
	59-0467	212.294	
	59-0468	213.289	
	59-0469	378.318	
	59-0470	325.293	
	59-0471	350.261	
	59-0472	351.249	

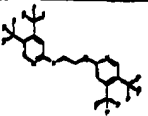
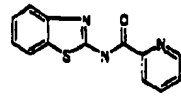
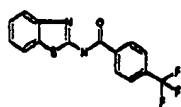
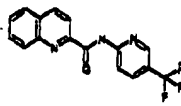
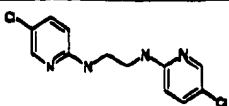
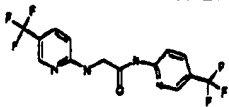
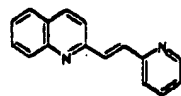
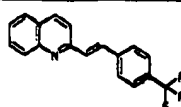
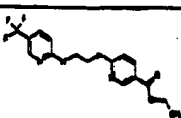
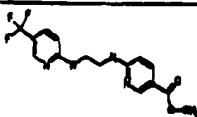
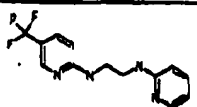
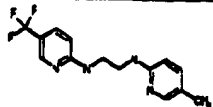
144/146

nand2

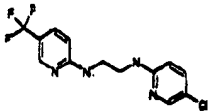
	59-0476	350.265	
	59-0477	283.256	
	59-0478	351.253	
	59-0479	283.258	
	59-0480	332.328	
	59-0481	363.26	
	59-0482	349.277	
	59-0483	307.278	
	59-0484	315.246	
	59-0485	250.3	
	59-0486	364.292	
	59-0487	302.298	

145 / 146

nand2

	59-0488	486.259	
	59-0489	255.3	
	59-0490	322.309	
	59-0491	317.269	
	59-0492	289.161	
	59-0493	364.248	
	59-0494	232.285	
	59-0495	299.294	
	59-0496	354.33	
	59-0497	340.303	
	59-0498	282.268	
	59-0499	296.294	

nand2

	59-0500	316.713	
---	---------	---------	--

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/18864

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS--structure

APS--diaryl, bone, osteo?, BMP

DIALOG--diaryl, bone, osteo?, BMP

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,441,964 A (BRYANT et al.) 15 August 1995, see entire document.	1-2, 5-28, 55-56
Y	US 5,523,309 A (BRYANT et al.) 04 June 1996, see entire document, especially claim 8.	1-2, 5-28, 55-56
Y,P	US 5,622,974 A (MUEHL) 22 April 1997, see entire document, especially claim 5.	1-2, 5-28, 55-56
Y	WO 93/10113 A1 (TEIKOKU HORMONE MFG. CO., LTD.) 27 May 1993, see entire document.	1-2, 5-28, 55-56
Y	WO 95/10513 A1 (PFIZER INC.) 20 April 1995, see entire document, especially claim 20.	1-2, 5-30, 55-56
Y	US 5,280,040 A (LABROO et al.) 18 January 1994, see entire document.	1-4, 31-43, 55-56

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 28 JANUARY 1998	Date of mailing of the international search report 26 FEB 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CELIA CHANG Telephone No. (703) 308-1235

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/18864

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chem. abstr. Vol. 127, abstract No. 127:17703, PETRIE et al. 'Preparation of (hetero) aromatic compounds for treating bone deficit conditions', WO-97/15308 (Eng.).	1-4, 31-43, 55-56
Y	Chem. abstr. Vol. 107, abst. No. 107:109578, WATTS et al. 'Studies on the ligand specificity and potential identity of microsomal antiestrogen-binding sites', Mol. Pharmacol. 1987, 31(5), 541-51.	1-2, 50-56
Y	Chem. abstr. Vol. 108, abstract No. 108:69162, JORDAN et al. 'Effects of antiestrogens on bone in castrated and intact female rats', Breast Cancer Res. Treat. 1987, 10(1), 31-5.	1-2, 50-56
Y	Chem. abstr. Vol. 115, abstract No. 115:8533, SCHWARZ et al. '1,2-diphenyl-1-pyridylbut-1-enes - potential antiestrogens. part 1. synthesis' Arch. Pharm. 1991, 324(4), 223-9.	1-2, 44-49, 55-56
Y	NEELAM et al. Structure-activity relationship of antiestrogens: A study using triarylbutenone, benzofuran and triarylfuran analogues as models for triarylethylenes and triarylpropenones. J. Med. chem. 1989, Vol. 32, pages 1700-1707, see entire article.	1-2, 50-56
Y	VON ANGERER et al. Studies on heterocycle-based pure estrogen antagonists. Ann. N. Y. Academy Sciences. 1995, Vol. 761, pages 176-191, see especially pages 178-180.	1-2, 5-28, 55-56

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/18864

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/18864

## A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6): A61K 31/165, 31/215; 31/33, 31/405, 31/415, 31/42, 31/425, 31/44, 31/47, 31/505, 31/53, 31/535, 31/54

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL : 514/222.5, 223.2, 223.8, 224.2, 226.5, 229.2, 230.5, 255, 258, 259, 296, 307, 311, 336, 345, 352, 354, 457, 365, 367, 374, 375, 385, 394, 396, 397, 415, 443, 535, 646

## B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/222.5, 223.2, 223.8, 224.2, 226.5, 229.2, 230.5, 255, 258, 259, 296, 307, 311, 336, 345, 352, 354, 457, 365, 367, 374, 375, 385, 394, 396, 397, 415, 443, 535, 646

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The claims are deemed to correspond to the species as listed in the following manner:

Group I, claims 3-4 and 31-43 compounds corresponding to Ar1 is condensed six membered heterocyclic ring, Ar2 is various aromatic rings;

Group II, claims 5-28, compounds corresponding to Ar1 is condensed five membered heterocyclic ring, Ar2 is various aromatic rings;

Group III, claims 29-30, compounds corresponding to Ar1 is isolated five membered heterocyclic ring, Ar2 is various aromatic rings;

Group IV, claims 44-49, compounds corresponding to Ar1 is isolated six membered heterocyclic ring, Ar2 is various aromatic rings;

Group V, claims 50-54, compounds corresponding to Ar1 is phenyl ring, Ar2 is various aromatic rings;

Group IV, claims 1-2, 55-56 in part (remaining compounds)

The following claims are generic: 1-2, 55-56

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2 and ANNEX B section (f), the species lack the same or corresponding special technical features for the following reasons:

The six groups of compounds corresponding to method of treating conditions of deficiency in bone growth, resorption or replacement using structurally distinctive compounds. Each group of compounds as delineated above does not share significant structural element (see Ar1, Ar2 and L are all variables, thus, not common element). In addition, at least one Markush alternative is found in CA 127:17703.